ARCHIVES OF OPHTHALMOLOGY.

HEMANGIOMAS OF CEREBELLUM AND RETINA (LINDAU'S DISEASE).

WITH THE REPORT OF A CASE.[1]

By DR. HARVEY CUSHING (BOSTON) and
DR. PERCIVAL BAILEY (CHICAGO)

(With eighteen figures, one in color, on Text-Plates XXII.–XXXI.)

ANGIOMAS of the retina have long been recognized by ophthalmologists under the name of v. Hippel's disease; cysts of the cerebellum have come to be frequently operated upon by neuro-surgeons and some of them prove to have an angiomatous nodule in their walls; cystic kidneys and cysts of the pancreas that have given no symptoms during life are occasionally found post-mortem by pathologists. That these and other lesions not uncommonly occur together in the same patient and constitute a disorder with hereditary tendencies has recently (1926) (27) been clearly shown by Arvid Lindau of Lund, which fact well justifies the eponym used in the title of this paper.

From a primary interest in the pathological nature of the cerebellar cysts, two examples with a hemangiomatous basis having come to his attention, Lindau was led to seek for similar specimens in the various pathological collections in Sweden and on the Continent with the result that fifteen unreported examples were assembled. In examining the post-mortem protocols of these cases, he was struck by the frequency with

[1] From the surgical clinic of the Peter Bent Brigham Hospital, Boston.

which the cerebellar cyst was associated with angiomatous and cystic lesions in other parts of the body.

One of the specimens, discovered in Stockholm (Lindau's Case 4), had been secured in 1922 from an autopsy, the records of which showed that in addition to the angiomatous cyst of the cerebellum, there had been found a bilateral adenoma of the suprarenal glands. The patient, moreover, had been known clinically to have had what was diagnosed as "an arteriovenous aneurysm" of the right retina for which the eye had been enucleated eight years previously, the specimen having been preserved without histological examination. When cut and examined microscopically a small capillary hemangioma of the peripheral retina was brought to view.

Because of this interesting disclosure, Lindau was drawn into a study of angiomatosis retinæ, a rare malady with a familial tendency and of which some fifty cases have been reported. In reviewing these cases, he found that approximately twenty per cent. of the patients had been known to have intracranial complications accounting for the tradition among ophthalmologists that v. Hippel's disease was a serious malady. In two of the cases, indeed (those of Czermak (9) and Seidel (35)), a post-mortem examination had served to show that death had been due to the effects of a coincidental cerebellar cyst.

Though previous observers, therefore, had observed this combination of retinal and cerebellar lesions, there was no reason to suppose that they were correlated until Lindau's studies brought to light the fact that additional changes in other organs were likely to be found: namely, cysts of the kidney and of the pancreas, hypernephromas, and occasionally multiple angioblastic tumors of the spinal cord. Evidently, therefore, here was a new and previously unrecognized disease.

Lindau succeeded in gathering from the literature and from unpublished pathological records fifteen examples of this disorder which he designated "angiomatosis of the nervous system." A year later in a second paper (28), written particularly to draw the attention of ophthalmologists to the subject, he announced that in the interim four additional examples had been disclosed at post-mortem examinations. One of these cases had been personally observed; information con-

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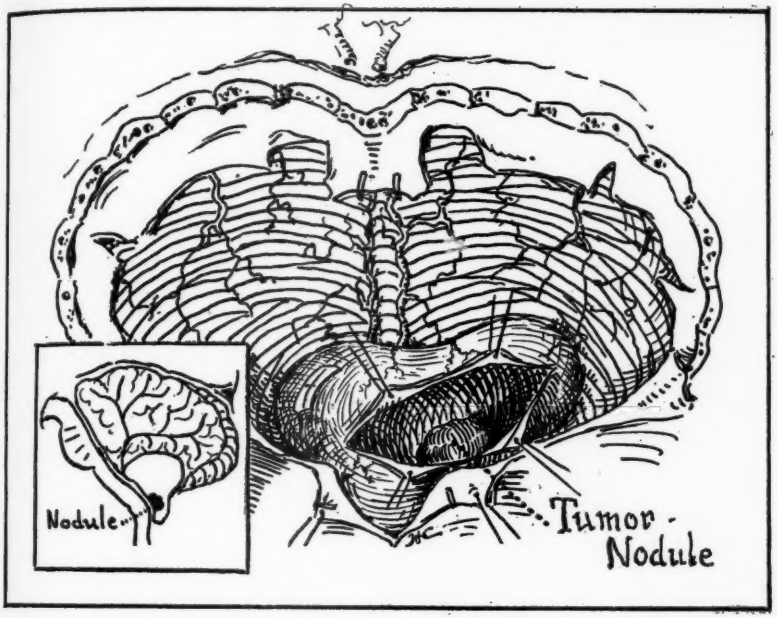

FIG. 1. Immediate postoperative sketch giving general appearance of operative field with cyst and position of nodule.

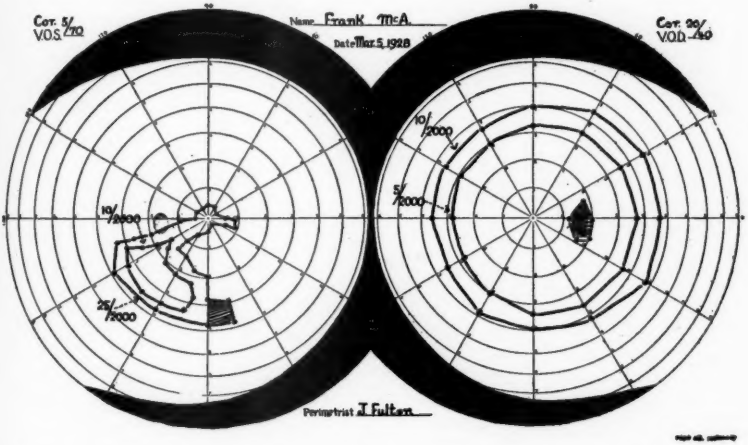

FIG. 3. The fields of vision (screen) five years after patient's operation in 1922. At that time there was no visual defect.

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FIG. 2. Drawing of the patient's eyeground. (Kindness of Dr. William H. Wilmer.)

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cerning the others had been supplied by Hammar (19) of Amsterdam, by Rochat and Tresling of Groningen, and by Wohlwill of Hamburg. The history of Lindau's personally observed case is briefly as follows:

> The patient, whose brother had previously died from a presumed cerebellar tumor, succumbed to an operation undertaken for comparable symptoms and at autopsy there was found a *cystic hemangioma of the cerebellum, cystic pancreas, cysts of the kidney, hypernephromas of kidney and similar appearing tumors of the epididymis.* A histological examination of the eye, in which nothing more than a choked disk had clinically been recognized, revealed a *hemangioma of the retina* of microscopic size.

The cases of Rochat (33) and of Wohlwill (37) have since (1927) been published and still another example, the twentieth, has been recorded by Shuback (36), a cystic hemangioma of the cerebellum having been found in association with a cystic pancreas and cystic kidneys in which were two small hypernephromas.

To these twenty cases we are able to add one more, it being the first one, so far as we are aware, in which the histological diagnosis of the cerebellar lesion has been verified during the life of the patient.

CASE REPORT.

On *December 8, 1922*, Frank McA., a truck driver, 30 years of age, entered the Brigham Hospital (Surg. No. 17893) with the chief complaint of suboccipital headaches which had begun without apparent cause about two months previously.

There was nothing notable in his past history apart from the fact that he was supposed to have had an attack of cerebrospinal meningitis in 1919.

In spite of some peculiarities of the clinical picture, notably astereognosis of the left hand and only a questionable papilloedema, he showed a sufficiently definite cerebellar syndrome (nystagmus, positive Romberg, unsteadiness of gait, etc.) to justify the diagnosis of a cerebellar tumor.

On *December 13th* in the course of the usual bilateral cerebellar exploration a low-lying and superficially placed cyst was exposed (Fig. 1). The cyst contained xanthochromic fluid and on opening it a small mural nodule of

tumor was found laterally placed about at the level of the foramen magnum in which it had become engaged. Though the tumor nodule was quite vascular, it was successfully excised.

The patient made an uneventful recovery and was discharged practically free from symptoms on *January 3d.*

The lesion was supposed to be a gliomatous cyst and the tissue was submitted to the pathological laboratory as a vascular gliomatous nodule, a gross diagnosis which received histological confirmation.

It was at about this time (1922) that we had begun to attempt a classification (1) of the gliomas on a clinico-pathological basis. In the course of this study we soon found that there were a number of tumors in the series that in the past, for want of proper differential stains, had been regarded as vascular gliomas which in reality were blood vessel tumors (hemangioblastomas), the tumor in the case of Frank McA. being one of them.

We were in process of assembling these particular tumors with the intent of publishing them when in reviewing the literature of the subject we came upon Lindau's monograph, the value of which for our immediate purposes, because of its somewhat misleading title "Studien über Kleinhirncysten," had been insufficiently appreciated. We in the meantime had identified among our series of tumors eleven hemangioblastomas of the nervous system, only four of which happened to be essentially cystic though all of them were located in the cerebellum; this was true also of the cases in Lindau's series, a fact which had led him to express doubts as to whether they ever occurred in the cerebrum. Three of our eleven cases had died from the effects of one or more operations and had come to autopsy without any abnormality other than the primary tumor or the effects of its surgical exposure having been disclosed, though it must be admitted that the spinal cord was not removed for examination nor were the retinæ examined. A fourth case died after operation and a fifth case some months afterward at home, neither of them with post-mortem examinations.

Though these five cases were beyond recall, we promptly set about to have the eyegrounds of the six surviving cases reexamined on the assumption that in our own examination of

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FIG. 4. Case of Scarlett. Note the angiomatous nodule in the lower part of the field, the beaded artery, the enlarged vein, exudation and detachment of retina.

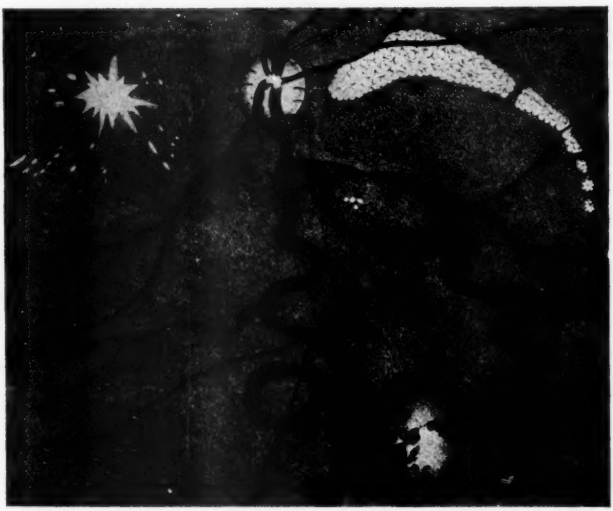

FIG. 5. The earliest illustration of a case of retinal hemangioma described as an arteriovenous aneurysm (Fuchs, 1882). Note the beaded artery to the right.

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FIG. 6. Wood's case (1892) of "retinal detachment with unusual dilatation of retinal vessels." Eye enucleated subsequently and examined by Treacher Collins (1894) who described the underlying lesion as a capillary nævus.

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the fundus, restricted largely to the papilla for evidences either of choked disc or of optic atrophy which rarely necessitates dilatation of the pupil, we had probably overlooked or failed to recognize an outlying angioma of the peripheral retina.[1]

As chance would have it, Frank McA. whose clinical history has been briefly given was the first to report and proves to be the only one of the five to show an unmistakable retinal angioma (Fig. 2). We are aware of course from Lindau's second paper that the lesion may be a microscopic one and early in its course may therefore not be discernible by ophthalmoscopic examination, but the positive finding in even this one of our patients has so interested us that we have felt impelled to give an account of the case independent of our study of the blood vessel tumors in general.

After the detection of the retinal lesion in this patient, a detailed review by Dr. J. F. Fulton of his family and personal history has brought out additional facts secured from an older sister as chief informant which may now be given:

Family history of "eye trouble" (first generation). The patient's father, who died at 36 years of age, had always had poor eyesight and wore "thick spectacles." For four or five years before his death he was largely confined to bed because of gastric symptoms, dizziness and inability to walk. There was disagreement as to whether he had stomach or brain trouble. He died suddenly in an attack of some kind and after an examination the attending doctor stated that death had been caused by rupture of a cystic tumor of the brain called a sarcoma.

An aunt is said to have died under very similar circumstances, also from "a ruptured cystic sarcoma" eight years previously, and it is recalled by members of the family that the doctor had commented upon the fact that it was peculiar both brother and sister should have died from such an unusual disorder.

Of the *second* (the patient's) *generation*, there are two sisters and one brother surviving. The older sister (the principal informant) is 45 years of age. She states that

[1] We wish to express our obligations to Dr. W. H. Wilmer of Baltimore, to Drs. E. T. Smith and A. L. Prince of Hartford, to Drs. H. H. Glosser and Park Lewis of Buffalo, and to Dr. George Derby of Boston who have kindly examined these patients for us.

the family inherit poor eyesight and all tend to have rather prominent eyes. She herself has had poor vision, particularly in the left eye, since childhood. She shows a high hypermetropic refractive error, the fundus being best seen on the right with a +5 and on the left with a +7 lens. She is given to recurrent suboccipital headaches, but the eye-grounds show no proliferative retinitis or evidence of an angioma.

The patient himself, when 8 years of age, because of poor vision was examined by Dr. Allen Greenwood who noted (1897) the high refractive error and prescribed glasses, but informs us that he made no notes of a fundus examination.

The second sister is now 30 years of age and was born with "ruptured tear ducts" but is said to have no particular trouble with her eyesight. (She has not been examined.) A brother died in infancy of unknown cause.

Third Generation. The patient has been married 21 years and has eight healthy offspring. The oldest child, a daughter aged 20, is married and has one infant child apparently with normal fundi. The second daughter, aged 19, has had eye trouble since childhood with recurrent suboccipital headaches. The eight children (6 girls and 2 younger boys, aged 7 and 9) have all been examined and though two of them show a marked hypermetropic error of refraction, no retinal abnormalities could be detected.

It may be too early in these children for the lesion to manifest itself, in which connection it should be noted that the cerebellar lesion in the eleven cases in our series and in those collected by Lindau did not show symptoms of its presence till the age of the patients averaged 34 years.

Past History. The patient's presumed attack of "cerebrospinal meningitis" has been carefully inquired into and doubts may be had of this diagnosis. It appears from the records of the hospital where he was confined that on *October 7, 1919,* while starting his auto truck, the crank "kicked," pressing his shoulder upward, causing pain and stiffness of the neck; that his symptoms chiefly of suboccipital headache, severe enough to require repeated doses of morphia, had come on abruptly. He showed retraction of the neck, a positive Kernig sign, and a lumbar puncture gave a bloody fluid in which a house officer is said to have found "intra and extra cellular diplococci." He was confined to the hospital for five weeks.

His attendant of the time admits that the clinical record is not very clear and it seems far more probable to us that the sudden symptoms were due to a traumatic rupture of the thin-walled cyst caught in the foraminal ring. From the time of this attack in 1919 to 1922 when he first came

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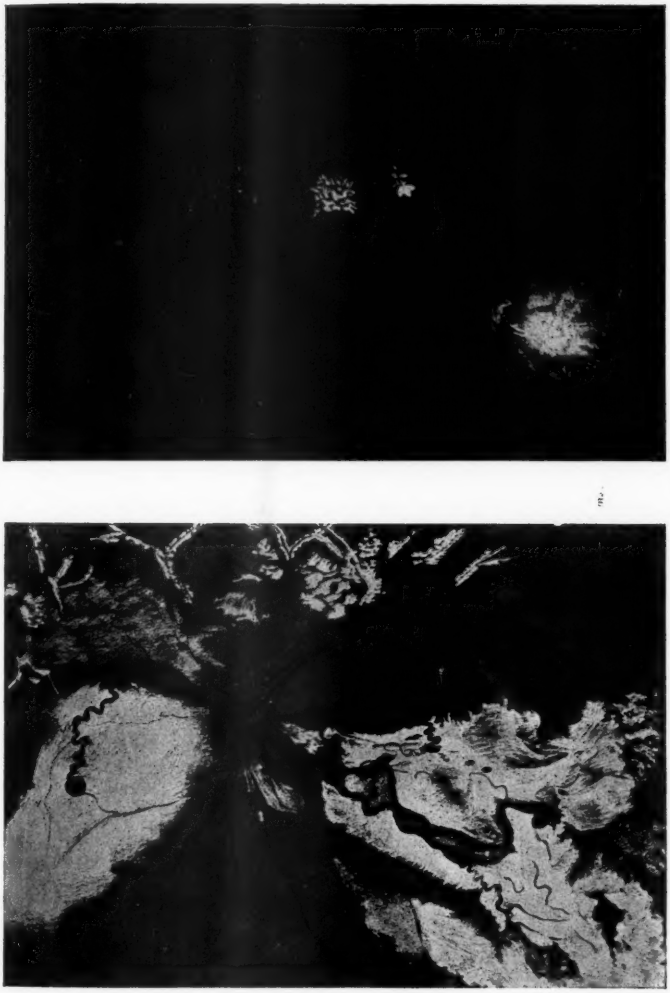

FIGS. 7 and 8. V. Hippel's Case 1 (Otto Meyer), showing advance of lesion from November, 1893, to March, 1896.

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under our care, he appears to have been comparatively free from discomforts, though in all probability a neurological examination in the interval would have shown some residual cerebellar symptoms.

Ophthalmological Notes. At the time of the patient's first admission to the Brigham Hospital in 1922, there was a difference of opinion among several observers as to whether there was a choked disc. It was recognized that there was a congenital refractive error. Haziness of the disk margins was noted and the presence of some new tissue formation which was ascribed as possibly a sequel of the supposed meningitis. One observer, while doubting the presence of tumor or pressure, noted, without mention of the eye involved, that there was an enormous vein which ran downward in a very tortuous course toward the lower retina. No particular significance was attached to this and none of the other five observers who gave notes from time to time on the condition of the eyegrounds made mention of the fact.

In 1924, a year or more after the patient's cerebellar operation, presumably owing to failure of vision, he was examined at the Massachusetts Eye and Ear Infirmary, where an ophthalmological examination must have been made, for it was noted that the retinæ were not detached; but the angioma was not detected.

Thus out of many examinations during the patient's life by at least eight observers, the presence of the angioma was not detected until on his readmission to the hospital for study on *March 1, 1928*, over five years after the cerebellar operation.

During this interval, vision in the left eye had become impaired and the house officer, Dr. Fulton, aware of our interest in Lindau's disease, quickly recognized that the large, tortuous vein previously noted was accompanied by what was an abnormal artery, the two passing out of vision, with the pupil undilated, in the lower periphery of the retina. In addition, the retina showed an extensive proliferative retinitis which certainly had not been present three years before, for it could hardly have escaped notice. The fields of vision taken before the operation in 1922 had shown no defects but at this time there was a marked distortion in the affected eye (Fig. 3.)[1]

[1] Fields plotted two months later, on May 16, 1920, show still further constriction, so that the process is doubtless rapidly advancing to blindness.

Dr. George Derby kindly saw the patient for us at this juncture and dictated the following note; certain of his statements that seemed to us of special interest we have taken the liberty of italicizing.

O.S. Posterior adhesion [iridocyclitis] of the iris to the lens at six o'clock. A dot on the posterior surface of the lens slightly on the nasal side. Except in the upper temporal quadrant the disc is blurred in outline owing to astigmatism, and below the outline cannot be distinguished. The vessels come out of the lower central part of the disc. The superior nasal artery is extremely small and divides into three branches which run upward. Two veins run upward also, one to the nasal side and one slightly upward toward the temporal side. There is a patch of pigment on the temporal margin of the disc; and off the edge of this, almost connecting with it, is a large irregular whitish patch (probably formation of fibrous tissue in the deeper retinal layers) with considerable pigmentation on the margin toward the nerve.

The temporal margin of this patch is irregular and sends two processes far out toward the periphery of the fundus. The vessels in this region seem to be in reasonably good condition. These patches show areas of pigmentation. The patch extends downward on the temporal side of the macular region and reaches down below it.

On the nasal side of the disc there is a similar fibrous patch which shows some pigment and marked irregularity of the edges extending out to the periphery as far as can be seen. These patches are underneath the retinal blood vessels.

The lower blurred margin of the disc shows two relatively enormous vessels. An *artery on the nasal side which is four or five times the normal size* passes through a rather œdematous area and at about one disk diameter below the disk its caliber narrows to the size of a normal artery. It then dilates again almost to its original size and runs downward and outward temporally until it crosses the vein perhaps three or four disc diameters below the nerve. *This artery shows a very characteristic beading in different portions of its course.*

The second vessel on the temporal side is a *vein of enormous caliber* which looks nearly twice as large as the artery and is quite tortuous in its course. This runs downward and slightly outward to the place where it passes under the artery. At this point it is possible to see that the

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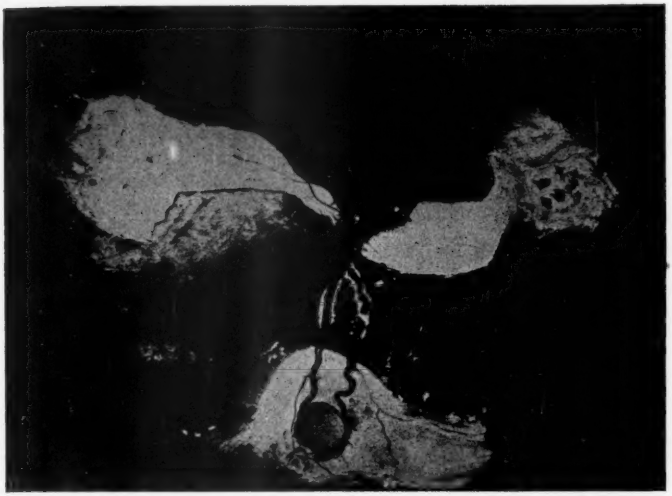

FIG. 9. V. Hippel's second case (Otto Mobius), showing typical "six o'clock" angioma with somewhat advanced retinal change.

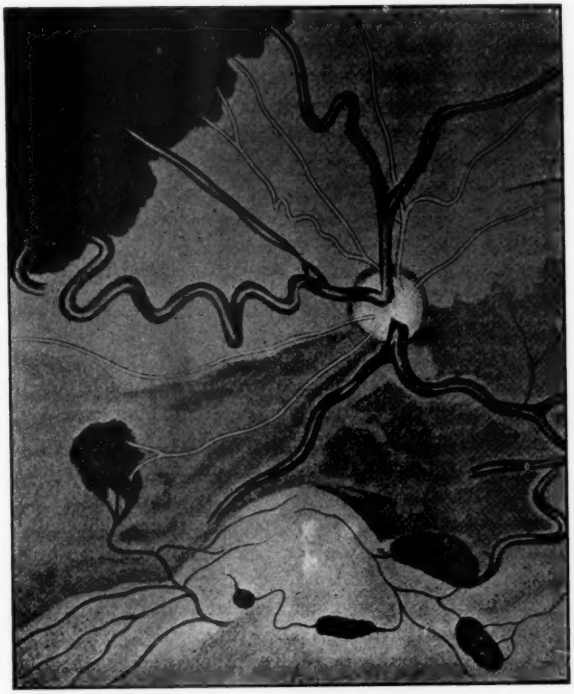

FIG. 10. The Goldzieher (1898) - Czermak (1905) case. The first case after Collins correctly diagnosed as a capillary hemangioma in spite of the highly advanced exudative process that led to the enucleation.

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artery makes a slight indentation on the vein. As the vessels lie alongside each other, *it is difficult to tell from their color which is artery and which is vein.*

At the point where these vessels cross, there is a pear-shaped patch of atrophy where the sclera shows through. There is a slight pigmentation on its nasal margin. The lower part of the retina shows a tigroid pigmentation. The artery after crossing the vein gradually becomes somewhat smaller and runs downward and temporally. The vein also runs downward in a parallel direction to the periphery and, at the limit at which one can see, *both vessels disappear in a prominent rounded nodule* which can be best seen with a +12 lens. It has some white fibrous tissue on its superior margin, but elsewhere has a pink color. The surface is covered with a number of small blood vessels. The mass appears fairly sharply localized. One cannot see how far forward it extends but from side to side it certainly is not over a disk diameter at this point. The upper border is hemispheric and it definitely protrudes from the underlying retina at least 2 or 3 D.[1]

There is an occasional cholesterin crystal seen in the central area, and on the nasal side also. Beautiful cholesterin crystals are seen above and in the macular region.

The disk is oval and within normal limits. *It is so badly outlined below that it almost looks like choking.* I can see no pulsation. The artery passing above it is undoubtedly small. The whole superior nasal artery which divides near the disc is very small and shows perivascular changes along most of its length whereas the superior temporal artery is of normal size.

O.D. Here the iris dilates normally; media are clear; nerve head is rather small with slight indentation on the nasal side above and below and rather pale on the temporal side with a shallow physiologic cup. Cilioretinal vessel at 8 o'clock; a faint choroidal ring on the temporal side of the nerve. The arteries in this eye are extremely small throughout. These have a silver wire reflex and a perivascular sheath runs along them for some distance from the disk, which is very marked on the lower temporal branch. Where they cross the veins there is a slight imprint made. The veins also seem to be perhaps a bit smaller than normal. Tigroid fundus.

Both the right and left eyes are best seen with a +9 lens.

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[1] In the color sketch of the fundus kindly made for us under Dr. Wilmer's direction, the lesion had been brought more fully into view by the aid of prisms.

Discussion.

A hemangioblastoma of the nervous system is a relatively benign lesion. It is important, therefore, that an ophthalmologist who finds one of these lesions in the retina should realize the need of looking for cerebellar symptoms, since a cerebellar tumor of like sort most favorable for operation may be coexistent. It is obviously no less important that a neurosurgeon, desiring to make so far as possible an exact pathological diagnosis of a cerebellar lesion before operation, should know of the existence of retinal angiomas and something of their appearance.

As *angiomatosis retinæ* was a condition quite unknown to us, we have been through the literature of the subject and venture to give a brief historical statement concerning it accompanied by a few illustrations of some of the better known examples[1] for the benefit of others who may be, as we were, similarly uninformed. So far as we are aware, the only case described in this country was reported in 1925 by Scarlett (34) (Fig. 4), who gives a typical illustration of the lesion after it has begun to cause secondary changes in the retina.

The first unmistakable example in the literature was clinically recorded in 1882 by Fuchs (14) who interpreted the ophthalmoscopic picture (Fig. 5) as an arteriovenous aneurysm. It is possible that even before Fuchs a far advanced case may have been observed and one eye studied anatomically by Panas and Rémy (1879) (31), the other eye of the same patient having been later described clinically by Darier (1890) (10) as a sort of retinitis proliferans. The true nature of the disease, however, was first recognized by Treacher Collins (1894) (7) who examined the eye of a patient with an advanced retinal lesion that had been briefly described and pictured (Fig. 6) two years before by Wood (1892) (38). Collins not only called attention to the familial character of the disease, for the sister of the patient was similarly afflicted, but concluded after a careful microscopical study that the essentia

[1] An excellent review of the subject to 1916 will be found in Prof. Th. Leber's article in the *Graefe-Saemisch-Hess Handbuch der Gesamten Augenheilkunde*, II Teil, Bd. vii, p. 1966–1994.

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FIG. 11. Pooley's case of "retinal angioma." Note beaded condition of artery.

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lesion was a "capillary nævus which in places had undergone cystic degeneration."

In the years following, an ophthalmoscopic description of other cases was given: by Goldzieher (1899) (17) who was obscure in his explanation of the pathology of the lesion; by von Dzialowski (1900) (13) who spoke of it as an "Aneurysmenbildung," and by Leplat (1901) (26) who likewise ascribed the appearance to a congenital arteriovenous aneurysm.

In 1904 v. Hippel (21) reported his two cases, the first of which (the patient Otto Meyer) had been shown at the Heidelberg Congress in 1895 as having "an unusual disease of the retina" without other explanation than that it might be retinal tuberculosis. This notable article was accompanied by a series of four excellent illustrations in color of the eye of Otto Meyer which show the advance of the process between the year 1893 (Fig. 7) when the lesion was first observed and 1896 (Fig. 8) by which time multiple foci had become apparent. The single illustration (Fig. 9) of the eye of v. Hippel's second patient (Otto Möbius) shows the condition to have been approximately in the same stage as that in our own patient.

It was not until seven years later that v. Hippel had an opportunity to gain, in one of these cases (Otto Meyer's), first-hand knowledge of the pathology of the lesion. Meanwhile, Czermak (1905) (9), just before his untimely death, had made a brief report of the microscopical study of the eyes of Goldzieher's patient, the lesion, in spite of its advanced stage (Fig. 10), having been shown to be a true capillary hemangioma.

Shortly after this, Coats in England published (1908) (5) his remarkable paper on exudative retinal disease, the last section of which is given over to a discussion of the later stages of the cases in question in which there was assumed to be an arteriovenous communication. That Coats was thought by others to have had the malady in question under consideration is shown by the fact that soon after (1910) another case, accompanied by an illustration in color of an unmistakable angioblastoma of the retina (Fig. 11), was reported in England by Pooley (32) who merely refers his readers to Coats' admirable description of advanced stages of the condition.

In 1911 appeared v. Hippel's second paper (22) containing an account of his own studies of one eye of the patient, Otto Meyer; and having meanwhile learned of the earlier findings of Treacher Collins, of Czermak and of Coats with which his own agreed, he chose, doubtless because of the multiple hemangiomas that were present (*Cf.* Fig. 8) to designate the condition *angiomatosis retinæ*. Shortly after this, in 1912, came Coats' second paper (6) on *Retinitis exudativa*, a perusal of which leaves one somewhat more confused about the conditions he is describing than did the last section of his first paper.

Between the years 1911 and 1921, though many clinical cases were reported [e.g., those of Moore (30) (Figs. 12 and 13) and of Ditróí (11–12) (Figs. 14 and 15)], confusion regarding the exact pathological nature of these angiomatous lesions was caused by the papers of Meller (1913) (29), of Ginsberg and Spiro (1914) (16) and of Guzmann (1915) (18), all of whom reported typical examples of the disorder but regarded the process, owing to the secondary changes which occur, as a gliosis or angiogliomatosis of the retina (*gliosis retinæ diffusa telangiectoides*). The confusion, in other words, was the same as that which has reigned in regard to the histopathological nature of the hemangiomas found in other parts of the nervous system, the excessive vascularity being regarded as a reactive rather than a primary incident in a gliotic process.

Meanwhile, however, Leber's excellent review of the subject had been published (1916) (25), the lesion in an early case (Fig. 15) had been subjected to study by Gamper (1918) (15), and finally the papers by Brandt (1921) (4) and by Berblinger (1922) (3) served definitely to establish the true pathology of the primary lesion. In one of Brandt's three cases, the eye had been removed sufficiently early to have been unaccompanied by the secondary exudative changes and gliosis that so often confuse the histological picture. The lesion happened to be a cellular rather than capillary type of hemangioma which he termed an "endothelioma," but his pictures show it to be a typical hemangioblastoma. Brandt correctly emphasized that the lesion was a true tumor which differed from the congenital angiomas in other parts of the body in that it did not begin to show clinical evidence of its presence until the third decade on the average.

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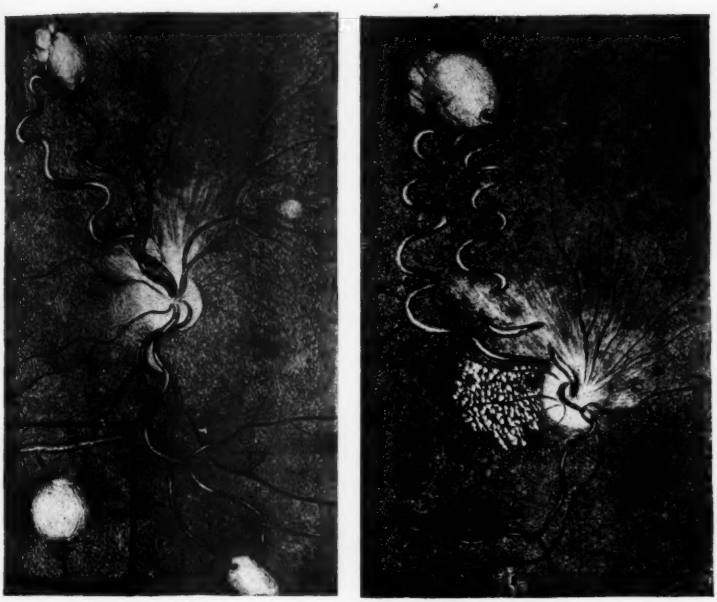
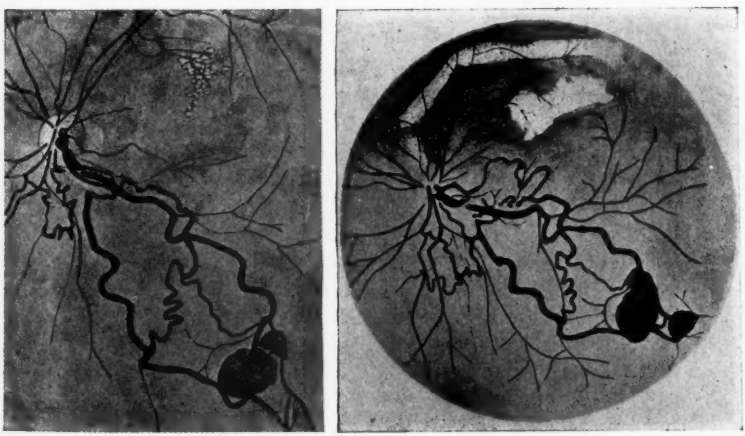


FIGS. 12 and 13. Moore's Case (1912) with bilateral angioma: left eye with multiple lesions; right eye with single lesion.



FIGS. 14 and 15. Ditrói's case showing slow advance in process between 1914 and 1919. Note increased vascularity with beaded condition of artery; fusion of former two nodules with an additional one appearing; increasing retinitis.

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Up to this point attention has been paid to the retinal lesions alone, but the story by no means ends here. In 1912 Seidel (35) in a report before the Ophthalmological Society in Heidelberg of a typical case (Fig. 17) in an early stage, called attention to a fact previously unemphasized: namely, that a cerebellar cyst had been found at autopsy in Czermak's patient, whereas his own patient, curiously enough, had developed a choked disc with cerebellar symptoms and a cyst had been demonstrated by puncture. What is more, it was known that the patient's brother had died after an operation for a cerebellar cyst. He pointed out, too, that v. Dzialowski's (1900) (13) patient had a choked disk and that a post-neuritic atrophy was recorded in Jakoby's (1905) (23) case.

Nearly ten years passed before this interesting observation appears to have been in any way supplemented. In the article by Brandt (1921) (4), to which we have referred, is described the necropsy on v. Hippel's original patient (Otto Meyer) who, seventeen years after being first observed, had died of intracranial symptoms. There was found in addition to a tumor of the right retina (the left eye had been previously enucleated), tumors of the tip of the right petrous bone, the convexity of the left cerebellar hemisphere, and of the cauda equina. These were taken to be metastatic from the eye but when examined microscopically appeared to be metastases from a malignant hypernephroma, although no primary hypernephroma was found in the region of the kidneys.[1] He decided finally that the tumors were probably neither metastases from the retinal tumor nor from a hypernephroma but that there was a simultaneous primary formation of numerous tumor nodules and that there was no necessary connection between the retinal tumors and the others.

A year later Berblinger (1922) (3) described another case (Fig. 18) in which an angioma of the retina was associated with multiple tumors elsewhere in the nervous system, one of them in the lower half of the medulla oblongata having been shown microscopically to be a typical capillary hemangioma. Heine (1923) (20) who examined the eye of Berblinger's patient did not escape from the confusion of many of his predecessors

[1] The close resemblance of the cells of certain of these hemangioblastomas to those of a hypernephroma has been pointed out by Lindau.

and concluded after a careful study that the tumor of the retina was an "angiogliosis"; he expressed himself as being more inclined to regard the case as an example of Coats' retinitis exudativa than of v. Hippel's disease. Berblinger, however, properly insisted that Heine's term angiogliosis fails to emphasize the essential character of the primary retinal lesion which he takes to be a hemangioma and of which the exudation and the gliosis are but a secondary irritative reaction; he believed that the tumors found in the eye and in the medulla were independent of each other and resulted from a dysontogenetic blastomatous growth.

Five years later (1926) appeared Lindau's illuminating paper (27) in which all of these obscurely associated observations were brought together and their true relationship clearly shown. He pointed out that in the examination of v. Hippel's original case Brandt (1921) had found, in addition to the lesions in the central nervous system which we have mentioned, cystic kidneys, cystic pancreas, and tumors of the epididymis, spleen and cartilages. He called attention to the fact that Koch in 1924 (24) in describing a cystic pancreas noted that there were present in the same individual cystic kidneys, cavernoma of the liver, and hemangiomas of the spinal cord and the cerebellum; also that in the Berblinger-Heine case a cystic pancreas was found.

Many other such cases, among which we may mention that of Bassoe and Apfelbach (1925) (2) as having been published in this country,[1] have also been picked up by Lindau from the literature and doubtless many more will follow now that attention has been drawn to the matter. And as was mentioned at the outset, three cases have been reported during this past year (1927) by Rochat (33), by Wohlwill (37) and by Shuback (36), the latter having for the first time used the eponym Lindau's disease.[2]

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[1] The medullary tumor was described by these authors as a glioma but has been shown by subsequent examination to be a typical capillary hemangioma.

[2] Of these three recent reports, that by Rochat is particularly noteworthy. It concerns a family in which in the first generation the mother died of an unknown lesion of the brain. In the second generation, of five children three brothers were affected, one with angiomatosis retinæ, and another

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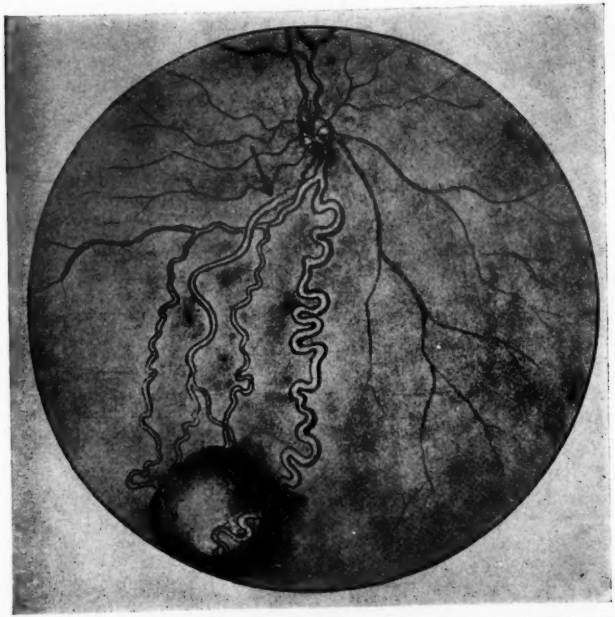

FIG. 16. Gamper's case (1918). Eye removed because of blindness with severe headaches (possibly cerebellar). Note hint of beaded condition of artery (arrow); lesion described as a telangiectasis.

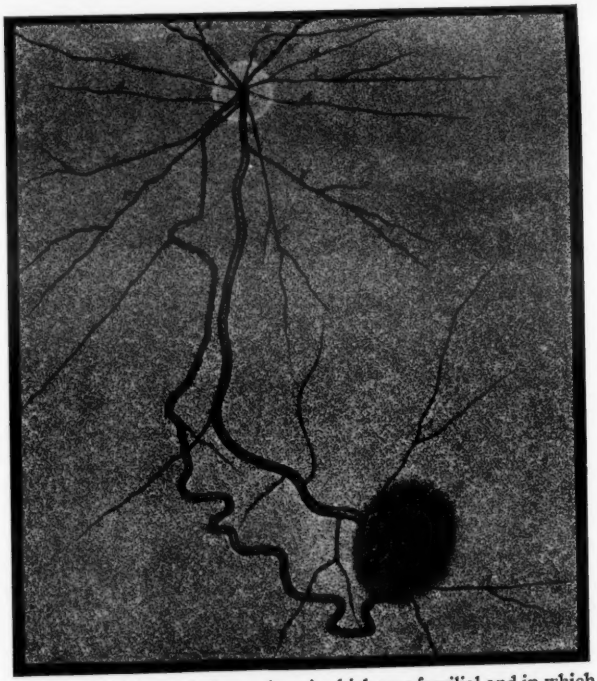

FIG. 17. Seidel's typical case (1912) which was familial and in which cerebellar symptoms were recognized. Note beaded artery.

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And so, as stated in the introductory paragraph, a variety of associated lesions, notable among which are cerebellar and retinal hemangioblastomas, have been assembled by Lindau in a pathological complex and placed upon a basis of maldevelopment of the mesoderm in the third fœtal month.

Conclusions. The typical picture of angiomatosis retinæ of v. Hippel consists of a pair of hugely enlarged vessels often emerging from the lower part of the disc to disappear in a small tumor mass in the peripheral retina. The vessels, though of approximately the same color, can be distinguished by the fact that the vein is the larger of the two, whereas the artery is often beaded and of varying caliber. Not infrequently in course of time other small tumors may appear in other parts of the retina with the development of a similar pair of vessels.

The process slowly advances with the ultimate occurrence of secondary changes in the shape of opacities and infiltrations due to exudative secretion and sometimes to hemorrhages, with the formation of a reactive gliosis, iridocyclitis, separation of the retina, glaucoma, and so on, which may necessitate enucleation. These secondary changes which fall in the category of Coats' proliferative retinitis ultimately serve to conceal the nature of the primary lesion. Both eyes are likely in time to become involved and the condition has been found in many cases to be familial.

Though the histological nature of the underlying lesion remained for a long time obscure, it is now known to be a hemangioblastoma, a form of tumor which exudes plasma and tends to produce cysts having xanthochromic fluid contents. It moreover has come to be appreciated that coincidental hemangioblastic cysts are not infrequently found in the cerebellum arising usually from an anlage over the posterior part of the IVth ventricle.

Lindau's studies have served to show that these angioblastic lesions of the nervous system are not infrequently found in

with cerebellar tumor. The third brother had an angioma of the right retina and died following an operation for cerebellar tumor. A necropsy was obtained but no mention is made of the condition of the abdominal organs. In the third generation, one boy has developed angiomatosis in both retinæ.

association with cysts of the kidney, cystic pancreas, hypernephromas and tumors of the adrenal glands.

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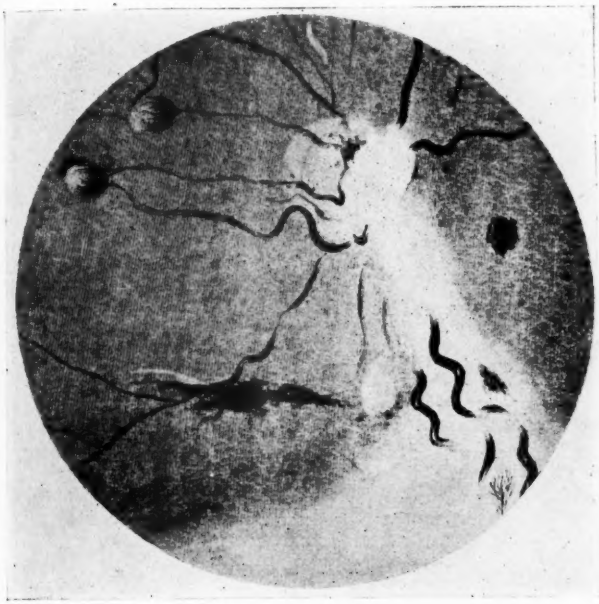

FIG. 18. Berblinger's case described by Heine (1923) as an inflammatory intraocular pseudotumor with retinal cysts; subsequently shown by Berblinger to be due to a capillary hemangioma.

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LENS PROTEIN—THE ISOLATION OF A THIRD (GAMMA) CRYSTALLIN.

By Dr. EARL L. BURKY and Dr. ALAN C. WOODS, Baltimore, Md.

(From The Wilmer Ophthalmological Institute, Johns Hopkins Hospital.)

IN our first study of the serological and chemical properties of lens protein, it was assumed that the Alpha and Beta crystallin fractions were the only constituents present. In a second communication dealing with new methods of preparation and concentration of Beta crystallin, we indicated the belief that there might possibly be a third substance in lens protein. It is the purpose of this paper to report the isolation of this fraction which we have arbitrarily called Gamma crystallin. This Gamma crystallin has been separated from the previous Beta fraction, of which it was a component part.

After precipitating out the Alpha crystallin from the whole lens protein in the usual manner, the filtrate (impure Beta) was dialyzed to pH 7.4, and then precipitated by acetic acid to pH 5.0, removing any remaining Alpha impurities. The resultant solution, presumably pure Beta crystallin, did not react with anti-Alpha serum. This Beta crystallin was now further purified, and concentrated in the usual manner by saturating with sodium chloride. The Beta crystallin was now precipitated by addition of 0.1% glacial acetic acid. This Beta precipitate was removed by filtration and dissolved with N/10 ammonium hydroxide, dialyzed free of sodium chloride, and cleared by Berkefeld filtration. There resulted a solution of Beta crystallin with a protein concentration of 3%. This concentrated Beta antigen, tested with the same anti-Alpha serum to which it had previously given a negative

reaction when in its unconcentrated state, gave now a weakly positive reaction in low dilutions of the serum. Puzzled by this change in the precipitin reaction with an Alpha serum, we studied this Beta antigen in this light.

The steps of this study were as follows: To this 3% Beta crystallin, (pH 7.4) was added acetic acid up to pH 6.0, which pH we had before found to be the iso-electric point of Beta crystallin. A voluminous precipitate resulted, which was removed, by filtration. Both precipitate and filtrate were now studied.

The precipitate was redissolved in N/10 ammonium hydroxide, dialyzed to pH 7.4 and precipitated at pH 6.0. This was repeated five times. The resulting solution was sterilized by Berkefeld filtration, and repeatedly injected into Rabbit 132. A serum resulted which gave a definite precipitation reaction with this, and other, Beta antigens, and gave no reaction to Alpha antigen. This crystallin fraction, with the iso-electric point of pH 6.0, is the Beta crystallin.

The filtrate which we preserved after precipitation of the above Beta crystallin at pH 6.0, and was kept in a refrigerator for one month to allow any remaining Beta crystallin to settle out. The supernatent fluid was then decanted. This was found to contain a protein concentration of 1%, which was precipitated by ammonium sulphate, in concentration over 50% saturation, indicating it was definitely albumen. This albumen is the "Gamma crystallin."[1]

This albumen fraction was now studied as to its antigenic properties by intravenous injections into animals, twice weekly for four weeks or more, in amounts up to 100*cc*. It appeared totally inert, failing to produce any specific precipitins. *In vivo*, therefore, it appears completely to lack antigenic properties. However, if tested against the Beta serum of the older type, which now must be considered an antiserum to a Beta-Gamma complex, or tested against the

[1] The Alpha and Beta crystallins, in their pure solutions, are precipitated by less than fifty per cent. ammonium sulphate saturation, indicating they are definitely globulins. The globulin fraction of Alpha and Beta are freely soluble in weak acid solutions, indicating they are pseudo-globulins.

whole lens antiserum, the pure Gamma fraction gives a definitely positive precipitin test *in vitro*, indicating that while it may be a satisfactory *in vitro* antigen, *in vivo* it acts only as an antigen when there is some accessory stimulus, such as would be supplied by Beta or Alpha fraction. The albumen fraction is optically active (Ad = 80), and therefore racemization cannot be considered as the responsible factor in the lack of antigenic activity. The Gamma is definitely a protein as shown by the insoluble coagulate formed by boiling. Its diminished antigenic activity *in vivo* is not remarkable, for numerous authors have noted the slight antigenic activity of albumens as compared with globulins derived from the same source.

Our studies to date, therefore, have shown that lens protein is composed of three immunologically distinct fractions. First, the Alpha crystallin which has an iso-electric point of pH 4.8. Second, the Beta crystallin which has an iso-electric point of pH 6.0. These two crystallins are pseudo-globulins, are antigenically active, are organ specific, and lack species specificity. Third, the last component is Gamma crystallin which is an albumen, with no iso-electric point in aqueous solution, and which lacks antigenic properties *in vivo*, when injected in animals in its pure state. With an accessory stimulus such as may be supplied by the other crystallins it is, however, capable of producing antibodies, and *in vitro* acts as a definite antigen. The Gamma crystallin was isolated from our former Beta crystallin and in the light of this finding, the Beta crystallin discussed in our former reports must now be considered a Beta-Gamma complex.

A STUDY OF THE RECESSION OF CHOKED DISKS FOLLOWING OPERATIONS FOR BRAIN TUMOR.[1]

By Dr. GILBERT HORRAX and Dr. CAMERON HAIGHT,
Boston, Mass.

SINCE choked disks are a frequent and characteristic evidence of brain tumor the protrusion of the disks in diopters, as measured with the ophthalmoscope, is one of the most useful methods in gaining some estimate of the amount of increase in intracranial tension. Conversely, after operations for the relief of intracranial pressure the measured recession of disk protrusion is a great help in determining the success of the procedure employed. The rapidity of this recession is due doubtless to many factors, such as the completeness of tumor removal, the degree of restoration to a more normal fluid circulation, the size and position of the growth, and its relation to the cerebrospinal fluid system. In an attempt to obtain information concerning certain of these factors for the purposes of this meeting a series of 100 cases has been studied. These represent a chronologically consecutive series of patients who have had verified brain tumors with papilledema. The estimations of choking in diopters in practically all instances were readings by more than one observer experienced in the use of the ophthalmoscope, and in all possible instances the same individuals' preoperative and post-operative estimations were used for a given patient. It is fully realized that the series is too small a one upon which to base more than the most general conclusions.

It seemed quite obvious that no useful information would

[1] From the surgical clinic of the Peter Bent Brigham Hospital.

Read at the annual meeting of the Association for Research in Nervous and Mental Diseases, New York, December 28, 1927.

be acquired by taking the series as a whole and estimating the amount and percentage of disk recession irrespective of the operative procedure and the site of the tumor. For this reason two primary groups were selected in order that more critical information might be obtained relating to some of the factors already mentioned. For further details Group I was also re-arranged as will appear. The same general scheme of recording averages was used in all groups, the method of arriving at these figures being as follows:

The height of the disks in diopters before operation for each patient was first obtained from the various readings. The number of days after operation until the disks became flat or the patient was discharged from the hospital was next determined. The amount of swelling present at the time of the patient's discharge,—usually nil, but in some instances 1 to 2 D was then subtracted from the pre-operative reading, the difference being the actual fall in diopters during the time elapsed. The percentage of fall was likewise calculated, as being a much more valuable figure than the amount of recession in diopters, inasmuch as a lowering of 1 diopter might mean anything from perhaps 20 to 50%. The general averages of each of these factors for all the patients in the various groups was then figured.

The first group (cf. Table I) comprised those patients from whom the tumor had been wholly or very considerably removed, and a decompression left in addition. The group was subdivided into cases with tumor above the tentorium and those with tumor below this structure, inasmuch as the mechanism producing intracranial pressure in these two sub-groups is essentially different.

In the supra-tentorial cases the average time after operation, until the disks had become flat or the patient was discharged from the hospital was approximately 20 days. In this time the disks fell an average of 2.9 diopters from a pre-operative average height of 3.5 diopters, or 80%. The greatest and most rapid fall in this group was 7 diopters in 21 days. In two patients there was a slight rise in the choking rather than a fall after operation, one of these tumors being an astrocytoma, the other being an astroblastoma.

In the sub-tentorial cases the average time was approximately

18 days, and the average fall was 3.1 diopters from an original average of 3.4 diopters or 91%. The greatest and most rapid fall was 6 diopters in 17 days, and in no case did the disks rise after operation.

TABLE I

GROUP I. *Complete or extensive tumor removal with decompression.*

a. *Supra-tentorial—40 cases*

Average height of disks before operation	= 3.5 diopters
Average fall after operation	= 2.9 diopters = 80.3%
Average time during which recession took place	= 19.8 days
Greatest and most rapid fall	= 7 D in 21 days

b. *Sub-tentorial—34 cases.*

Average height of disks before operation	= 3.4 diopters
Average fall after operation	= 3.1 diopters = 91%
Average time during which recession took place	= 17.8 days
Greatest and most rapid fall	= 6 D in 17 days

As a comparison to the foregoing the second group was taken (cf. Table II), being composed of patients upon whom the operation amounted practically to a decompression, a few fragments of tumor having been removed for identification. In the supra-tentorial cases of this group an average time of 18.7 days elapsed during which the disk swelling subsided, an average of 1.9 diopters from an original average of 3.0 diopters or 63.3%. The greatest and most rapid fall was 5 diopters in 13 days. In one case the disks rose after operation,—a frontal astrocytoma. In the sub-tentorial cases, the average time was 18.4 days, and the fall was 3.8 diopters from an original average of 4.5 diopters, an average of 84.4%. The greatest and most rapid fall was five diopters in 16 days.

TABLE II

GROUP II. *Decompression without tumor removal*

a. *Supra-tentorial—15 cases.*

Average height of disks before operation	= 3.0 diopters
Average fall after operation	= 1.9 diopters = 63.3%
Average time during which recession took place	= 18.7 days
Greatest and most rapid fall	= 5 D in 13 days

b. *Sub-tentorial—11 cases.*

Average height of disks before operation	= 4.5 diopters
Average fall after operation	= 3.8 diopters = 84.4%
Average time during which recession took place	= 18.4 days
Greatest and most rapid fall	= 5 D in 16 days

Comparing these two groups there are perhaps two points worthy of comment, namely that the lowest average disk recession (63.3%) is in cases of decompression for tumors above the tentorium without tumor removal, *i.e.* sub-division "a" in Group II, and that the greatest average disk recession in percentage (91%) occurs in patients who have had sub-occipital decompressions for tumor below the tentorium, with complete or extensive tumor removal, *i.e.* subdivision "b" in Group I. The latter is perhaps what might be expected from the release of an obstructive internal hydrocephalus.

To gain an idea as to whether the general situation of a tumor made any particular difference as to the rate of disk subsidence the cases in Group I were arranged in what we have termed Group III. Here the supra-tentorial cases were divided into frontal, parietal (central), temporal and occipital, and the sub-tentorial into intra- and extra-cerebellar.

The figures may be best followed in tabular form as shown in Table III.

TABLE III

GROUP III. *Complete or nearly complete tumor removal with decompression.*

a. *Supra-tentorial*

1. *Frontal*—11 cases

Average height of disks before operation	= 3.4 diopters
Average fall after operation	= 2.9 diopters = 85%
Average time during which recession took place	= 23 days
Greatest and most rapid fall	= 5 D in 20 days

2. *Parietal* (central)—16 cases

Average height of disks before operation	= 4.0 diopters
Average fall after operation	= 3.3 diopters = 82%
Average time during which recession took place	= 17.5 days
Greatest and most rapid fall	= 6 D in 21 days

3. *Temporal*—8 cases

Average height of disks before operation	= 3.0 diopters
Average fall after operation	= 2.2 diopters = 73.5%
Average time during which recession took place	= 17.7 days
Greatest and most rapid fall	= 5 D in 23 days

4. *Occipital*—5 cases

Average height of disks before operation	= 2.2 diopters
Average fall after operation	= 1.6 diopters = 71%
Average time during which recession took place	= 18.8 days
Greatest and most rapid fall	= 3.5 D in 19 days

b. *Sub-tentorial*

1. *Intra-cerebellar*—20 cases

Average height of disks before operation	= 3.2 diopters
Average fall after operation	= 2.9 diopters = 89%
Average time during which recession took place	= 17.0 days
Greatest and most rapid fall	= 5 D in 19 days

2. *Extra-cerebellar*—14 cases

Average height of disks before operation	= 3.4 diopters
Average fall after operation	= 3.3 diopters = 96%
Average time during which recession took place	= 18.5 days
Greatest and most rapid fall	= 6 D in 17 days

In this grouping the extra-cerebellar tumors (mainly acoustic neuromas) show the greatest average disk recession after operation, namely 96% of their average original choking, this figure being well above those in this or any other group.

For the last table we have again re-arranged Group I with reference to the rate of disk recession in some of the more frequent types of tumor. (cf. Table IV).

TABLE IV

GROUP IV. *Complete or nearly complete tumor removal with decompression.*

a. *Supra-tentorial*

1. *Glioma*—21 cases

Average height of disks before operation	= 3.6 diopters
Average fall after operation	= 2.6 diopters = 72.8%
Average time during which recession took place	= 18.5 days
Greatest and most rapid fall	= 5 D in 15 days

2. *Meningioma*—15 cases

Average height of disks before operation	= 3.7 diopters
Average fall after operation	= 3.9 diopters = 78.6%
Average time during which recession took place	= 18.2 days
Greatest and most rapid fall	= 6 D in 21 days

b. *Sub-tentorial*

1. *Glioma*—14 cases

Average height of disks before operation	= 3.4 diopters
Average fall after operation	= 3.0 diopters = 89%
Average time during which recession took place	= 19.1 days
Greatest and most rapid fall	= 5 D in 19 days

2. *Acoustic tumors*—11 cases

Average height of disks before operation	= 3.5 diopters
Average fall after operation	= 3.3 diopters = 95%
Average time during which recession took place	= 17 days
Greatest and most rapid fall	= 5 D in 31 days

3. *Medullo-blastomas*—6 cases

Average height of disks before operation	= 3.0 diopters
Average fall after operation	= 2.2 diopters = 72.7%
Average time during which recession took place	= 24.7 days
Greatest and most rapid fall	= 4 D in 23 days

No very significant features result from this grouping although in the sub-tentorial division medullo-blastomas tend to lag well behind the other ordinary tumors in the rate of disk recession. Supra-tentorial gliomas and meningiomas show no marked disparity in the subsidence of choking.

Summary.—From a study of choked disks before and after operation in a small series of 100 cases of verified brain tumors the following general statements seem warranted.

1. Decompressive operations for tumors both above and below the tentorium, with or without tumor removal are followed by a marked recession of the preoperative papilledema.

2. The disk recession after decompressive operations is most complete in patients with sub-tentorial tumors which

have been extensively removed, and is least complete in patients with supra-tentorial tumors which have not been removed.

The authors wish to acknowledge their appreciation to Dr. Harvey Cushing for permission to study these cases from his clinic.

EYE CONDITIONS IN LEUKEMIA.[1]

Report of Four Cases.

By Dr. BENJAMIN SACHS, Boston, Mass.

A REVIEW of the literature of the past twenty-five years shows that various eye involvements have been met in leukemia. The most commonly reported are changes in the fundus such as retinal hemorrhages, vitreous hemorrhages, retinitis, retinitis proliferans, distended veins, optic atrophy, optic neuritis, thrombosis of the central vein, and occasionally the whole fundus assumes a yellowish hue. Spontaneous hemorrhages in the lids and from the iris and ciliary body have also been reported. Only rare mention is made of involvement of the uveal tract, and no corneal complications have been reported at all.

In 1911 Hudson, of the Royal London Ophthalmic Hospital, reported that eye changes are found in 25% of patients with leukemia. In 1914, Koyanagi made a histological examination of eyes of four myelogenous and two lymphatic leukemias. He found the blood vessels of the choroid over-filled with lymphocytes.

In 1922 Bab reported a case of leukemia in which there was glandular enlargement in the neck and groin with fibrinous iritis and synechiæ. An iridectomy was followed by the formation of a hypopyon composed entirely of lymphocytes.

Tribenstein, in 1920, enucleated an eye because of a tumor in a patient who had leukemia. The ciliary body and iris were found to be infiltrated with lymphocytes, the choroid was also markedly involved, and tension was increased.

[1] From the Department of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

Cassolino reported a case of myologenous leukemia with uveitis. In a one-year-old child with acute lymphatic leukemia, Glinski found unilateral exophthalmos, an infiltration of the conjunctiva, ocular muscles, lacrimal organs, and uveal tract.

Brandt, a few years ago, studied the blood picture in thirty-eight cases of iritis. He met one leukemia. The patient had a leukocytosis of 120,000 with 99% small lymphocytes. X-ray treatment to the spleen reduced the leukemia and cured the iritis.

Because of the scarcity of eye involvements in leukemia reported, it was thought worth while to put the following cases on record.

CASE NO. 1. Miss C. R. C. Age 66. Early in 1925, a diagnosis of malignant lymphoma was made by Dr. George Minot. The patient had enlarged glands in the neck and a mass in the chest, there was also a questionable mass in the abdomen. The rest of the physical examination was negative. The teeth had been extracted previously, and X-ray of the gums showed no pathology. The throat and nose, urine and Wassermann were negative. There was a gastric history which might have suggested gall bladder disease. There was pronounced constipation. The blood picture showed no definite leukocytosis, and the differential count showed a relative increase in large mono-nuclear cells. X-ray treatment reduced the glands in the neck as well as the masses in the chest and abdomen.

In April, 1925, the eyes began to be inflamed. On examination by Dr. E. E. Jack, it was found that there was an iritis in both eyes with many posterior synechiæ. Atropine and dionin were prescribed. Later, cincophen was added. Under treatment, many of the synechiæ were freed, but at the end of May, another acute attack of iritis occured, and now deposits on the posterior surface of the cornea and anterior surface of the lens became evident. Vision, at this time, was about $\frac{1}{10}$ in each eye. The eyes continued to fail steadily. Dr. Walter Lancaster, found on slit lamp examination, large deposits on the cornea and lens, also some nodules, not of the Koeppe type, on the iris near the margin. The vitreous was very hazy because of floating opacities. A re-examination of the gums and nose and throat was again found negative. In addition to the local eye treatment, the patient now received typhoid vaccine without any improvement.

In the meantime, further X-ray treatment was given for the control of the Hodgkin's disease. In January, 1926, attention was given to the question of constipation. High colonic irrigations were given for several months. The patient felt that the eyes improved after this new treatment. Objectively, however, there was no change for the better. Both irides were extensively bound down, and the pupil areas occupied by exudate. There was a question of increased tension in the left eye. Vision now was only shadows, and fields taken with flashlight seemed good. In June, 1926, the patient was seen by Dr. G. S. Derby. At that time, the process was still active, and it seemed that projection was questionable upward. The prognosis was quite poor. Dr. Derby suggested doing an iridectomy in both eyes with the hope of being able to do something more later.

In December, 1926, the eyes were quiet and Dr. Lancaster did a preliminary iridectomy in the left eye, and later an intracapsular extraction of the lens, and in the right eye, a combined extracapsular lens extraction. In March, 1927, an iridotomy was done in the right eye. Her vision now with correction is $\frac{6}{60}$ in the right eye, and $\frac{6}{30}$ in the left eye. She is able to read evening newspapers, and her eyes are quiet.

Case No. 2—Miss L. A. Age 48. Patient of Dr. F. T. Lord. In June, 1926, she complained that over a period of about a year she had been having a dull aching pain in the left upper quadrant of the abdomen two or three times a week. On examination, she was found to be well developed, rather obese. There were enlarged glands on both sides of the neck, varying in size from peas to walnuts. The axillary glands and those in the groins were enlarged. The spleen was much enlarged.

The red count was over five million, and the white count 103,000. The blood smear showed 99% lymphocytes. The rest of the physical examination was negative including teeth, nose, throat, urine, and Wassermann. Under exposure to X-ray, the white count had dropped by October, 1926, to 18,000 and the blood smear showed 60% lymphocytes, and 40% polynuclear cells. The red count was five million. In May, 1927, the white count was again up to 49,000 with 91% lymphocytes.

At this time, she began to be troubled by blurred vision. The patient then consulted Dr. Verhoeff who had examined her several times before. Her eyes were negative, and the vision was normal on several occasions up to May, 1927. At this time, she complained of an irritation in the left eye.

Dr. Verhoeff found a Descemetitis. The vitreous was clear and vision was normal. On May 12, the eye was worse. The pupil was slightly larger, the choroid negative, and the vitreous clear. On the 17th, the Descemetitis was increased. Patient was now using 1% atropine. On the 26th, the eye was worse, and the tension was 35 by Souter's tonometer. The cornea was steamy. The patient was now given 2% pilocarpin every two hours. On June 1, tension was 33, and vision was $\frac{1}{10}$. On July 1, the tension was normal, the vision was $\frac{1}{10}-$. The eye was quiet, but Descemetitis was marked. On July 21, the vitreous was filled with fine opacities. There was a question of slight cupping of the disk. Tension was 20. In August, the eye became inflamed. The aqueous was cloudy. Descemetitis was marked, vision was $\frac{1}{10}+$, and tension was 20. At the end of August, vision was $\frac{1}{10}$, tension 18, and there was no congestion, but there was no change in the uveitis.

Case No. 3.—Mrs. W. M. C. Age 46. Patient of Dr. G. S. Derby. In May, 1926, the vision was $\frac{5}{5}$ in each eye. The history at that time was that she had trouble with reading and sewing, and that the left eye was blurred in spells. The fundi were normal except for a few thread-like vitreous opacities. The vessels were of a light color, and the macular reflex absent. She was then being treated for a myologenous leukemia.

In January, 1927, the left eye became painful and blurred, and in March, when she was seen again, her right eye seemed to be normal, but the vision in the left eye was only fingers at two feet. Examination of this eye showed a gray reflex, a separation of the retina in the temporal side, a muddy iris, and a deposit at the bottom of the anterior chamber. The slit lamp showed many cells in the anterior chamber, slight bedewing of the surface of the cornea, many precipitates on the posterior surface of the cornea, dilation of the blood vessels in the iris, pupil adherent practically all the way round with sharp jagged synechiæ. The lens was clear, no fundus details could be made out, and tension was normal to touch. She was given cocain and dionin. A week later, the vision was the same, but the eye felt better. There was less injection, the iris was muddy, the cornea looked a little clearer, and there was still a small hypopyon in the anterior chamber. She was then sent to a hospital to be built up. While at the hospital, she received high voltage treatment over the spleen. Afeer this treatment, her blood picture improved considerably, and symptomatically, she was much better; and what is also interesting, her eye seemed to give her very much less

trouble and looked a good deal better. The patient died in July, 1927.

Case No. 4.—Miss E. L., 28. Patient of Dr. G. S. Derby. In 1918, patient first showed swelling on the left side of the neck and a diagnosis of Hodgkins was made. This was later confirmed by a microscopic study of an excised gland. Radium treatment was given with improvement. In 1920, the patient had infantile paralysis affecting both arms. The glands in the neck flared up again. She was again given radium with improvement. Her physical examination, including teeth, sinuses, throat, urine, and Wassermann, proved to be negative. In 1923 and up to 1927, she would have a flaring up of the glands in the neck and also enlargement of the mediastinal glands. For this, she had X-ray treatment.

Her ocular history is as follows:—In 1920, the vision was $\frac{6}{6}$ in each eye with correction. In 1921, vision as well as fundi were normal. In the winter of 1922, she had sore eyes. In September, 1924, there was a superficial keratitis in the left eye with an infiltrate at the edge of the cornea. There was also eczema of the nose. She was given atropine and 1% yellow oxide of mercury ointment, and the eye improved. In October, the right eye showed some roughening of the cornea. During that month, there was a flare up in both eyes with many small herpetic-like staining areas, there was no anesthesia. The eyes showed no change until December when the left eye became much worse with the formation of a deep ulcer of the cornea. In January, 1925, there was a flare up again in the right eye with a dendrite-looking process in the cornea. The eyes improved gradually, and in April, her vision in the right eye was $\frac{6}{9}$, and in the left eye $\frac{6}{60}$. There were a few flare ups up to June. At this time, she had some X-ray treatment for her glands, and her vision improved in the right to $\frac{6}{6}$ and in the left to $\frac{6}{15}$. In September, she again had some roughening of the cornea, but it improved rapidly. In January, 1926, both corneæ showed superficial vessels. In March, there was a staining area in the right cornea. In April, vision in both eyes was $\frac{6}{6}$ with correction, and both eyes were quiet, but in July, the left eye flared up again, and vision was reduced to $\frac{6}{9}$.

Summary.

The ophthalmic literature regarding leukemia and eye complications has been reviewed. Only few cases of uveitis have been found, and no mention is made of keratitis. The

three cases of uveitis and one case of keratitis reported in this paper were collected in one locality. No definite proof about the relation between leukemia and the eye involvements can be given, but no other known etiologic factor could be found, and in two cases, there seemed to be an improvement in the eyes, coincident with the general improvement of the leukemia following X-ray therapy.

In conclusion, I wish to thank Drs. Derby, Verhoeff, Lancaster, Minot, and Lord for their kind suggestions and help in preparing this paper.

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SOME ANALYTICAL OBSERVATIONS ON THE VITREOUS HUMOR FROM NORMAL AND GLAUCOMATOUS EYES.

By Major C. NEWCOMB, F.I.C., I.M.S., and Lieut. Col. R. E. WRIGHT, I.M.S., Madras.

THE part played by the vitreous body in a large proportion of the cases of chronic primary glaucoma has claimed attention in the Government Ophthalmic Hospital, Madras, for some years. It was customary to regard numbers of these patients clinically as posterior segment cases, meaning thereby that some change in the vitreous had determined the increase of tension.

In 1925 the following series of analyses were undertaken with a view to determining if any gross changes could be detected in the composition of the vitreous humor in such glaucomatous eyes and some observations were made on this work in the Annual Report of the hospital for that year, but the details were not published.

It was thought that perhaps in glaucomatous eyes the osmotic pressure of the eye fluids, especially of the fluid in the meshes of the vitreous frame-work, was increased and an attempt was made to try this. The experiments were inconclusive. They were made before our ideas on the possible physico-chemical equilibria in the eye had been clarified by Duke Elder's work. The detailed results may perhaps be of use to others working on this subject, and hence they are now presented.

The total solids, ash, and chlorides, were chosen for determination as being easy to do accurately on small quantities of material and as giving a general indication of the constitution of the vitreous.

It is unfortunate that there are only two samples of normal vitreous in the series, but for obvious reasons this is more difficult to obtain than glaucomatous vitreous.

Method. The vitreous was drawn in a syringe through an opening in the sclerotic and squirted into a weighed stoppered tube. The tube with the vitreous was weighed and then the contents washed into a platinum dish and dried in an oven (at 96°C.) and vacuum desiccator to constant weight (*i.e.*, constant to within 0.2*mg*). The residue was ashed, with care to avoid overheating, and the ash weighed. The ash was then extracted with nitric acid and the chlorides in it determined by Volhard's (micro) method.

Controls. The method was controlled by parallel analyses on the same sample of horse's vitreous, with the following results:

No.	*Amount of vitreous*	Mgrms. per Gram of Vitreous		
		Total solids	*Ash*	*Chl.*
1	0.8835	13.4 ± 0.5	8.8 ± 0.6	3.53 ± 0.06
2	0.5055	13.8 ± 1.0	.....	3.54 ± 0.05
3	0.7580	13.5 ± 0.7	8.7 ± 0.4	3.54 ± 0.05
4	0.7125	13.6 ± 0.7	8.8 ± 0.4	3.53 ± 0.06

These results are mostly consistent to within 0.2*mg* in weighing and 0.02*cc* in titration, but the errors shown (both in this table and throughout) are for 0.5*mg* in weighing and 0.1*cc* in titration. It was thought that errors in sampling might affect our results and to check this some of this same sample of horse's vitreous was filtered through a dry paper and the more fluid part (filtrate) and the less fluid part (residue) were analyzed separately with the following results:

	One Gr. of Vitreous Gives		
	Total solids	*Ash*	*Chl.*
	mgs	*mgs*	*mgs*
Filtrate.....	13.0 ± 0.4	8.7 ± 0.4	3.54 ± 0.05
Residue.....	14.0 ± 0.4	8.8 ± 0.4	3.54 ± 0.05

This indicates errors in sampling will have no effect on the ash and chloride and only a slight (and probably negligible) effect on the total solids.

The effect of overheating in ashing is shown in the following series of parallel determinations:

	Ash *mgs/grm vit*	*Chlorides* *mgs/grm vit*
1. Not ashed	.....	3·53 ± 0.06
2. Ashed at below red heat	8.8 ± 0.6	3.60 ± 0.06
3. Ashed at dull red heat	8.3 ± 0.6	3.33 ± 0.06
4. Ashed at bright red heat	6.9 ± 1.0	2.85 ± 0.10

In the weighings care had to be taken to weigh quickly as both the total solids and ash were hygroscopic. In the final weighings the weights were put on the balance correct to the nearest milligram before the dish was taken from the desiccator and the exact weight then calculated from three swings. In this way the error from gain of weight while weighing was not more than 0.1*mg* and practically constant.

At first sight it might seem that the average figures for the glaucomatous vitreous suggest an increased concentration as compared with normal. In view, however, of the wide divergencies in the figures for the separate analyses and the paucity of the analyses of normal vitreous this is not a sound conclusion.

What they do show is:

1. That different eyes vary considerably in the constitution of their vitreous.

2. In some cases (Nos. 8 and 10) the solids not ash (*i.e.*, presumably, mostly proteins) may be very greatly increased without a corresponding increase in the inorganic constituents.

No.	Date of receipt	Weight of vitreous grams	ONE GRAM OF VITREOUS GIVES			Ash as per cent. of total solids
			Total solids mgs	Ash mgs	Chlorides mgs	
			Normal vitreous			
1	8. viii. 25	1.033	13.4 ± 0.5			
2	16. xi. 25	0.576	13.5 ± 0.8	7.1 ± 0.8	3.28 ± 0.11	53 ± 7
			Glaucomatous vitreous			
3	15. ix. 25	0.282	16.0 ± 1.7	7.1 ± 1.8	.....	44 ± 12
4	—do—	0.460	13.0 ± 1.1	6.5 ± 1.1	these nine taken together 3.52 ± 0.06	50 ± 8
5	2. x. 25	0.4075	12.3 ± 1.2	6.1 ± 1.2		50 ± 10
6	6. x. 25	0.4165	13.2 ± 1.2	8.4 ± 1.2		64 ± 10
7	8. x. 25	0.4065	13.5 ± 1.2	8.6 ± 1.2		64 ± 9
8	22. x. 25	0.649	22.4 ± 0.8	8.5 ± 0.8		38 ± 4
9	29. x. 25	0.460	14.1 ± 1.1	7.6 ± 1.1		54 ± 7
10	4. xi. 25	0.438	21.7 ± 1.2	8.0 ± 1.2		37 ± 6
11	5. xi. 25	0.456	14.3 ± 1.1	9.8 ± 1.1		68 ± 8
12	—do—	0.322	17.1 ± 1.6	10.9 ± 1.6		64 ± 10
13	19. xi. 25	0.380	16.0 ± 1.4	8.7 ± 1.4	4.08 ± 0.17	54 ± 9
14	—do—	0.4385	14.5 ± 1.1	6.2 ± 1.1	2.46 ± 0.13	43 ± 7
15	24. xi. 25	0.368	14.7 ± 1.3	8.1 ± 1.4	4.10 ± 0.16	55 ± 10
16	1. xii. 25	0.5085	12.8 ± 0.9	8.3 ± 0.9	4.03 ± 0.11	65 ± 7
17	—do—	0.442	14.7 ± 1.1	9.1 ± 1.1	4.06 ± 0.14	62 ± 8
18	16. xii. 25	0.521	14.0 ± 0.9	8.6 ± 1.0	4.32 ± 0.11	61 ± 7
19	12. i. 26	0.493	14.4 ± 1.0	8.3 ± 1.0	4.44 ± 0.12	58 ± 7
20	21. i. 26	0.3725	12.9 ± 1.3	7.0 ± 1.3	3.92 ± 0.16	54 ± 11
21	2. ii. 26	0.415	11.6 ± 1.2	7.9 ± 1.2	3.95 ± 0.14	69 ± 10
22	16. iii. 26	0.307	14.3 ± 1.5	8.5 ± 1.6	3.91 ± 0.20	59 ± 11
23	15. iv. 26	0.451	12.8 ± 1.1	8.4 ± 1.1	3.92 ± 0.13	66 ± 8
24	—do—	0.3305	12.4 ± 1.5	8.2 ± 1.5	3.74 ± 0.19	66 ± 12
25	—do—	0.4405	15.2 ± 1.1	8.2 ± 1.1	3.68 ± 0.14	54 ± 8
			Average for glaucomatous vitreous			
	.....	.....	14.7	8.12	3.74	55

The errors shown are for 0.5*mg* in the weighings and for 0.1*cc* in the titration of the chlorides.

A CASE OF HEMANGIOMA OF THE CHOROID.

By Dr. S. B. MARLOW, Syracuse, N. Y.

(With one illustration on Text-Plate XXXII.)

THE presence of an unusual ophthalmoscopic picture and the rarity of the condition found seem to justify the recording of the following case:

H. V., age 19, medical student, was first seen July 23, 1923, when he stated that for more than a month he had noticed that his judgment of distance had become defective. More recently he had noticed that things had a greenish tinge with his left eye alone and that although weak—the vision of this eye never had, he thought, been as good as the right,—it had grown much worse.

Except for measles, influenza, and head colds he had always been well. He denied venereal infection. He had two healthy brothers but a sister had pulmonary tuberculosis.

Examination showed the right eye to be normal, vision $\frac{6}{6}$. There was a large "port wine" colored capillary nævus on the left side of the forehead which extended mesially practically to the mid-line, to the hair-line above, irregularly on the temporal side and included the whole upper lid below. There were a number of small dilated veins in the bulbar conjunctiva. The anterior segment appeared healthy, the pupil reacting normally. Vision of this eye was reduced to $\frac{6}{60}$, cycloplegic revealing 5D of hyperopia. With the pupil dilated the macula did not appear normal. This region seemed somewhat lighter in color than the R, more hyperopic than the disk and finely striated. Its appearance suggested detachment of the retina although the vessels were not distorted.

A month later the area of apparent detachment had spread. The retina itself was possibly somewhat more

ILLUSTRATING DR. S. B. MARLOW'S ARTICLE, "A CASE OF HEMANGIOMA OF THE CHOROID."

Angioma of Choroid. Section through thickest portion of tumor, showing structure of choroid replaced by large, thin-walled, communicating blood channels.

opaque, vision with correction reduced from $\frac{6}{12}$ to $\frac{6}{18}$. The field of vision was full but contained a relative scotoma about 10° in diameter just below the fixation point. The just limits of the blind spot were indefinitely irregular.

A thorough physical examination, including an intradermal tuberculin test, was negative at this time.

Five months later further deterioration had occurred. An extensive retinal detachment was present below. It had a peculiar grayish green appearance and the retina about the disk appeared to be crowded over its temporal margin. Corresponding changes were present in the field of vision.

The rapid progress of the case and the finding of Lawford's case report, although the fundus in his case was obscured by secondary cataract, suggested the diagnosis of angioma and the desirability of enucleation. He was asked to see a consultant for a second opinion. A diagnosis of deep retinitis was made owing to the peculiar slatey color of the detachment, the accompanying œdema of the retina and distinct congestion of the retinal vessels.

The consultant recommended that the patient be put to bed and a tuberculin test be carefully carried out. This was done with negative results. Examination of his nose and throat indicated an infected antrum and diseased tonsils. The antrum was opened and his tonsils removed.

While in the hospital confined to bed the retinal detachment grew progressively worse and patches of retinal exudate appeared. Vision became reduced to hand motion. As treatment was without benefit he was discharged from the hospital and continued his medical studies.

He was seen at intervals during the next three years, the right eye remaining normal. The left eye slowly deteriorated, a secondary cataract developing.

In April, 1926, a foreign body was removed from the left eye. He returned in June stating that ever since April this eye had been red and irritated at times. There was slight pericorneal congestion, the pupil was dilated nasally but reacted indirectly to light. The lens appeared swollen. Tension 43*m* (2/7.5).

The slit-lamp showed definite epithelial œdema and a grayish dusty change on the endothelium of the cornea. Miotics controlled the tension for about eight weeks when pain with increased inflammatory reaction recurred. Enucleation was advised and accepted, a glass ball being implanted in Tenon's capsule.

The eye was placed in formalin and after considerable delay sent to Dr. F. H. Verhoeff to whom I am indebted for the histological description.

DR. VERHOEFF'S REPORT.

Angioma of the Choroid
Diagnosis: Secondary Glaucoma
Complicated Cataract.

Microscopical examination of the cornea showed this to be normal. The filtration angle is blocked by the root of the iris. Extending from the false angle over the surface of the iris for a considerable distance is a new formed vascular membrane. The iris is undergoing fibrosis. The ciliary body shows little change. The lens shows an anterior capsular cataract, and anterior and posterior cataractous changes. The choroid is almost completely and uniformly replaced by large thin walled sinuses containing blood. In the vicinity of the optic disk it is from .025*mm* to .037*mm* in thickness. As it is followed anteriorly it gradually tapers out and the blood spaces are seen to occupy chiefly the inner layers of the choroid and to compress the ciliary body and the presence of similar sinuses in this region indicates that they are invading this structure.

The sinuses are of varying size and shape, elongated and oval, no round sinuses being present, no doubt as a result of the fixation. Some of the largest are .025*mm* in greatest diameter. Their walls are thin, composed of a single layer of endothelial cells, the endothelial wall of one sinus often being in contact with the endothelial walls of adjacent sinuses. In places there is some intervening connective tissue in which pigment cells are enmeshed. In this, arteries are occasionally seen. Frequently the sinuses communicate with each other. Bruch's membrane, the pigment epithelium, and the chorio-capillaris are for the most part intact, but near the optic disk the chorio-capillaris has been destroyed and the pigment epithelium shows proliferative and degenerative changes. The retina is completely separated, the subretinal space being filled with serum. It shows the degenerative and proliferative changes commonly found in separated retinæ.

COMMENT.

The literature has been recently reviewed by Lent and Lyon in connection with the report of their case. To this review the case of Mulock-Houwer should be added.

As pointed out by Lent and Lyon the clinical diagnosis of this condition from its very nature is difficult. The presence of vascular nævi in other parts of the body in nearly fifty per cent. of the cases must be considered important clinical evidence. The occurrence of retinal changes with a separation of the retina beneath which there is a serous exudate can very well be confusing. However, when these two findings, other nævi and an ophthalmoscopic picture of deep retinitis, are present the diagnosis of hemangioma of the choroid would seem justified clinically.

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PROTEIN THERAPY—SPECIFIC AND NON-SPECIFIC —IN OPHTHALMOLOGY.[1]

By Dr. ALAN C. WOODS, Baltimore.

BOTH specific and non-specific protein therapy are designed to stimulate the factors of immunity and resistance against disease. In specific protein therapy, the protein employed is one directly or indirectly related to the etiological factor causing the morbid process, it is used to evoke factors of resistance specific for the exciter of the disease. In non-specific therapy the protein employed is one in no way related to the etiological exciter of the disease, it is designed to increase the general resistance of the individual to disease and infection in general.

The history of specific therapy for the prevention and cure of disease is one of the most interesting stories in the progress of medicine. Modern specific therapy begins with the use of smallpox virus by Jenner, it progresses with the experiments of Pasteur on rabies and anthrax, the discovery of tuberculin by Koch, the discovery of diphtheria antitoxin by Roux and Behring, on to the developments of our own time. Early in the story we find ophthalmologists attempting courageously, yet uncertainly, to apply in their specialty the principle that "like cures like."

The history of the use of specific therapy in ophthalmology is long, and it is useless to trace it here. In the main, it has come down to four separate phases—about which there is still a great diversity of opinion. These four phases are, first, the use of tuberculin, secondly, the use of bacterial vaccines and derivatives, thirdly, the use of uveal pigment

[1] Read before Ohio State Med. Assoc., May 11, 1927.

in sympathetic ophthalmia, and fourthly, the use of lens protein in diseases of the lens. Each of these subjects has been widely discussed and presented. It is the purpose of this thesis to set forth briefly the present status of specific and non-specific protein therapy in ophthalmology.

Tuberculin Therapy.

The use of tuberculin in ophthalmology began shortly after its discovery by Robert Koch in 1891. The results reported from different clinics have been conflicting, varying from records of brilliant achievements to records of complete disaster. The disasters are sometimes so appalling, that one readily understands the remark of one of our most eminent tuberculographers, "while tuberculin is one of the most potent weapons in tuberculosis, yet the results following its injudicious use, make one believe all considered, that the world would have been better had it never been discovered." Yet the general confidence in tuberculin appears to be growing, and justifiably so. Without going into the controversy over its use, it may be of interest to describe briefly the method which has been adopted in the Wilmer Institute of the Johns Hopkins Hospital.

The object in the diagnostic use of tuberculin is to determine whether or not an unusual degree of tuberculin hypersensitivity exists, and at the same time avoid a focal reaction in the eye, which may be disastrous to the eye we are attempting to save. The intradermal diagnostic test has been routinely adopted. Intradermal injections in the forearm are made with 0.05*c.c.* of different dilutions of tuberculin—1:1,000,000; 1: 100,000; 1: 10,000, and 1: 1,000, making the intradermal dose respectively 0.00005*mgm.*, 0.0005*mgm.*, 0.005*mgm.*, and 0.05*mgm.* The smaller doses are first given, the larger doses only when the reactions to smaller doses are negative. The normal individual reacts to a dilution of a 1: 1000, or 0.05*mgm*, intradermally. A positive intradermal reaction with a 1:10,000 dilution is suspicious of an active tuberculous focus in the body, while a positive reaction with 1: 100,000 or a 1: 1,000,000 dilution appears to be pathognomic of an active tuberculous lesion. Whether this lesion may be in the suspected eye,

must be decided by the clinical appearance, and the absence of other etiological factors, as may be revealed by the general medical survey. We have never encountered focal reactions in the eye from this intradermal use of tuberculin.

If the process is believed to be tuberculous, and tuberculin therapy is decided upon, the primary dose is adjusted in relationship to the degree of hypersensitivity found. Thus, if the patient reacts to a 1: 1,000,000 dilution intradermally, the primary dose is 0.000001*mgm.* subcutaneously. If he reacts only to weaker dilutions, the usual primary dose is 0.00001*mgm.* The dose is then increased in the usual manner, the eye being carefully watched, and if any untoward reaction is observed in the eye, the next dose is sharply cut, and then again increased in the usual manner, the eye being carefully watched for any further reaction.

By this use of tuberculin, which is not at all original or unusual, remarkable and convincing therapeutic results are frequently observed, while in no instance have any untoward results, attributable to the use of tuberculin, been observed. The following is a typical case of tuberculin therapy.

Case 1.—W. C., age 26. Patient was first seen January 24, 1925, with a recurrent hemorrhagic retinitis, right vision = $\frac{20}{100}$ and the left vision = $\frac{20}{15}$. The right fundus showed several fresh hemorrhages and evidence of recent hemorrhages, with macular involvement. The left eye showed evidence of one recent hemorrhage in the nasal fundus. A complete medical survey revealed only moderately infected tonsils and a marked tuberculin hypersensitivity, the patient reacting to 1: 1,000,000 intradermal tuberculin. The tonsils were first removed without effect on the ocular disease. While under observation, before tuberculin therapy was started, a mass about 1½ disc diameters in size, with a surrounding zone of hemorrhage, formed in the right macula. This had every appearance of a true retinal tubercle. Tuberculin therapy was started with an initial dose of 0.000001*mgm.* given every fifth day, and increased in the usual manner. The treatment was well tolerated. There were no further hemorrhages, and gradual absorption of the central mass and hemorrhage in the right fundus took place. The patient's vision rose to $\frac{20}{15}$ eccentrically, while the left vision remained at $\frac{20}{15}$. In February, 1926, after the process had been entirely

quiet for six months and a dose of 8.0*mgm*, of tuberculin had been reached, the treatment was discontinued. In October, 1926, the patient returned with several fresh patches of hemorrhage and exudate in the right eye, and one fresh spot in the left fundus. Tuberculin hypersensitivity had returned. The right vision was reduced to $\frac{20}{100}$, the left vision remaining at $\frac{20}{15}$. Tuberculin therapy was again begun, and was tolerated without reaction. Within three months all signs of activity disappeared and the lesions became atrophic. Right vision rose to $\frac{20}{70}$ and the left vision remained at $\frac{20}{15}$. The patient is still under treatment.

The points to be emphasized in the use of tuberculin are these: 1. Great care should be exercised in the diagnostic use of tuberculin to avoid focal reactions. 2. The initial dose of tuberculin should always be very small, and graduated in relationship to the degree of hypersensitivity. 3. Tuberculin therapy should be instituted only after all manifest foci of infection have been eradicated, and should not be started until the patient has recovered from the effect of the eradication of such foci of infection. 4. After treatment has been finished, the patient should be watched for a return of the hypersensitivity.

Vaccine Therapy.

The large literature, discussions, theories and experiments on bacterial vaccine therapy, while of great historical interest, need concern us little here. Bacterial vaccines have been tried in a great number of ocular conditions, and with one exception, have proved of little value. The exception appears to be the treatment of furunculosis of the lids and adnexa, and of blepharitis, with autogenous vaccines of staphylococcus aureus. This has at times given brilliant results, yet in as many instances, failure has been equally conspicuous. It seems a "hit or miss" procedure, and is in line with the observation that staphylococci and streptococci are extremely poor antigens.

Recently, however, new applications of vaccine therapy have been opened up by the observations of Besredka, on the anti-virus of staphylococci and streptococci, and the experiments of Carrère on the eye with these bacterial filtrates.

Besredka showed there were two substances in the staphylococcus—one a "thermolabile virus" which is adherent to the body of the bacterium and which may produce serious skin lesions; the other is atoxic, thermostabile, and is easily detached from the body of the germ and antagonizes the former substance." This last substance he calls the anti-virus. He further showed that the application of this anti-virus to the receptive cells successfully vaccinated the cells, and rendered them immune to a subsequent lethal dose of the bacteria. Carrère then studied the application of this idea to the eye. He found that the instillation of the anti-virus in the conjunctival sac twenty-four or forty-eight hours before, protected the conjunctiva, cornea and anterior chamber of the eye against what was otherwise a fatal inoculation of the specific bacteria. The eye was not protected, however, against an intravitreous injection. A protective intravitreous injection of the anti-virus was necessary to accomplish this. In other words, by local application of the specific anti-virus the tissues of the eye were vaccinated and could be protected against an inoculation of bacteria, otherwise fatal to the eye.

This fact was soon employed in ocular therapy, and the French literature already carries reports of brilliant results obtained in blepharitis, dacryo-cystitis, conjunctivitis, and such conditions, by the application and instillation of the anti-virus specific for the bacterium causing the morbid ocular condition. Carrère believes these brilliant results are due to a local desensitization of the receptive cells. Besredka carries the theory slightly further. He points out that in the reaction between a virulent bacterium and the receptive cells, a third substance is liberated, as a product of the secretion and disintegration of the bacteria. This substance repels the phagocytes—a negative chemotaxis,—allowing the bacteria to multiply. Besredka believes that the application of the anti-virus has the function of accustoming the receptive cells, dulling their sensitiveness, to the bacterium—or, in other words, immunizing the cell. Thus the reaction between the receptive cells and the bacterium is abolished, negative chemotaxis is avoided, and normal phagocytosis takes place.

Whatever may be the theoretical explanation, the attrac-

tiveness of this therapeusis cannot be discounted, and promises a definite application in ophthalmology.

The recent studies of Mackenzie and Hanger, and others, on the allergic reactions from bacterial toxins, while not yet applied in ophthalmology, may ultimately open up new fields for the application of vaccines or bacterial filtrates in the endogenous infections of the eye.

Uveal Pigment Therapy.

This subject has recently been summarized and presented, and there is little to be added. In our experience a hypersensitivity to uveal pigment has commonly been found in active sympathetic ophthalmia. Others have not found this hypersensitivity so regularly. It seems that this failure may be due to inherent difficulties with the antigens, and also to a lack of full comprehension of the type of the reaction. The intradermal injections should be so given that there is, with all dilutions, a perceptible amount of pigment visible beneath the superficial cuticle. Erythema coming on in a few minutes should usually be ignored. It is usually traumatic, or may possibly be due to a reaction to a contamination of the antigen with beef serum. This should be controlled. Only in the extremely hypersensitive does a positive pigment reaction occur within the first few hours. As a rule the erythema around the site of the injection occurs from the eighteenth to the twentieth hour and persists from four to ten hours, then fading away. If the patient is not carefully watched during the forty-eight hours following the intradermal injections, a definitely positive reaction may easily be missed.

Ten patients, all with outspoken sympathetic disease and hypersensitive to pigment, have been treated with intramuscular injections of uveal pigment. These cases were reported in detail at the Meeting of the English Speaking Ophthalmologists in London in 1925. This pigment therapy appeared to be of very definite value in the treatment of the disease, and there appeared to be no contra-indication to combining its use with the usual therapy advocated for the treatment of the disease.

Since the publication of this report, one of the patients (No. 5 in the series) has been operated for the cataract which formed during the disease. The uneventful healing which followed operation was remarkable, especially when it is considered that the operated eye had suffered from sympathetic disease. The final result was as follows: The media was entirely clear, the fundus showed old scars from the sympathetic choroiditis, involving the macula, but $\frac{20}{70}$ vision resulted, from what at first appeared to be a hopeless eye.

This same remarkable healing was also noted in patient No. 9 of this same series, who was operated upon immediately after a long course of pigment therapy. This patient finally obtained $\frac{20}{30}$ vision. Not only does it seem apparent that pigment therapy is of value in the disease, but it also seems to influence very favorably the post-operative recovery in sympathetic ophthalmia, when operation is necessary.

Lens Protein Therapy.

This subject is in a highly controversial status. A brief review of the history will best show this.

Uhlenhuth, in 1903, found lens protein had the peculiar immunological property of organ specificity. A few years later Roemer was attracted by this observation, and thought this property might in some way be related to the etiology of senile cataract. Roemer did an immense amount of work, even giving cataract patients lens protein by mouth. His results were entirely inconclusive, but convinced him some immunologic action of lens protein was concerned in the etiology of cataracts. Verhof and Lemoine, in 1922, published their original observations on endophthalmitis phacoanaphylactica, apparently clearly showing a relationship between lens protein hypersensitivity and the inflammatory reactions developing after some operative procedures on the lens. Gifford, in 1925, reported a series of observations and experiments. He felt that endophthalmitis phacoanaphylactica, in the sense of Verhof and Lemoine, did occur. Yet the majority of reactions occurring in eyes, when lens protein was left free for absorption, were due to an inherent toxicity of lens protein, possibly a protein split product of autolysis. Rotth reported animal experiments and clinical observations

on this same subject. From somewhat suggestive, yet unconvincing, experiments Rotth drew rather broad conclusions, —stating "there is no autohypersensitivity or autoanaphylaxis within the boundaries of possibilities in human pathology." Rotth believes endophthalmitis phacoanaphylactica has no existence. In a reply Verhof criticizes both Rotth's experiments and conclusions. Davis, reporting first in 1922, but stating that his investigations had begun many years previous, has used injections of lens protein as a therapeutic procedure in the treatment of cataract. His reasoning—that the production of specific antibodies may neutralize a toxin acting on the lens—is far from convincing, yet his results lead him to the belief that such treatment is of distinct value. In the discussion of this subject other observers do not appear to share this view. Much more startling than these clinical observations, illustrating a possible relationship between lens protein and cataract, are the brilliant experiments of Guyer and Smith. These observers, by the injection of fowl anti-lens serum in pregnant rabbits, and by the discission of the lens of pregnant rabbits, have produced cataracts in the eyes of the young.

On this laboratory side, Jess and Morner have shown that the lens is composed of different fractions, the alpha and beta crystallines, and have investigated the relative occurrence of these fractions. Hektoen has shown first that these are precipitinogenically distinct and has, in the main, substantiated Uhlenhuth's work.

Thus, in brief, stands the complicated situation. It is quite clear however, that lens protein is most complicated material. It seemed possible to us that a more careful study of lens protein might be profitable. Accordingly for the last two years, in collaboration with E. L. Burky, a study has been made of the chemical and immunological properties of lens protein. The first report of these studies is now in press. Lens protein appears to be chiefly of a globulin nature. We have finally succeeded in separating the alpha and beta fractions in a serologically pure state. These two fractions are absolutely distinct in their actions as antigens, as Hektoen before indicated. Both are organ specific. Neither has any species specificity. The isolated beta fraction has a tendency

to spontaneous precipitation, which tendency is apparently inhibited by the presence of the alpha fraction. We are not yet prepared to advance any statement concerning any relationship of these fractions to clinical hypersensitivity. As concerns whole lens protein, true clinical hypersensitivity apparently occurs. Further, unless the very greatest of care is exercised in the preparation of lens protein antigens, and in the controls for the intradermal test, false positives may occur. We have already encountered several such reactions. When these patients were controlled by skin test with beef aqueous, beef serum, and other such controls, and again tested with lens protein, which had been proven serologically pure, it was found these false positives were due to impurities in the original lens preparation;—the patients reacting to the controls and not to the serologically pure lens protein. Whether or not non-specific positive reactions, in the sense implied by Gifford, occur, cannot yet be said.

Concerning the therapeutic administration of lens protein for the prevention and absorption of cataracts, we have no experience. Nor does it seem wise to hazard any opinion in a subject where there now exists so little evidence for its rationale.

Our very limited observations on endophthalmitis phacoanaphylactica appear to confirm the original observations of Verhof and Lemoine. A few patients have been observed who gave definitely positive skin reactions to lens protein. One of these was in a child where a former discission had been followed by a severe ocular reaction. The patient was desensitized before the second operation and the post-operative course was entirely uneventful.

One very remarkable case of hypersensitivity was observed, which appears to extend further the possible rôle lens protein may play in the causation of delayed post-operative inflammation. This case was as follows:

CASE 2.—J. W., age 64. The clinical diagnosis was bilateral posterior cortical cataracts, reducing vision to $\frac{20}{100}$. The patient was given a complete medical survey, including skin tests with lens protein, before operation. The survey, and lens protein intradermal tests, were entirely negative. Operations by Dr. W. H. Wilmer were preliminary iridec-

tomy, cataract extraction four weeks later, and a discission six weeks after extraction. Operations were entirely uneventful. Primary healing was uneventful except for the development of a drug reaction to atropin. Vision of $\frac{20}{15}$ resulted two weeks after the discission. At this time the patient developed a uveitis of the utmost severity, with heavy posterior corneal deposits, turbidity of the vitreous, definite papillo-œdema, and vision reduced to $\frac{20}{200}$. The most exhaustive survey revealed no evidence of systemic disease or focal infection. The uveitis became better, and then relapsed. Finally, skin tests with both lens protein and uveal pigment were done, and the patient was found extremely hypersensitive to both these organ specific eye proteins. The hypersensitivity to lens protein had certainly developed after operation, for before operation a similar test was negative. When what is known of pigment hypersensitivity is considered, it seems probable the pigment hypersensitivity also developed after operation, but this cannot be said definitely, for there was no control pigment test prior to operation.

The patient was at once given desensitizing courses of both lens protein and uveal pigment. There was no additional treatment other than hot compresses to the eye. The eye rapidly cleared and there were no further attacks of uveitis. The posterior corneal deposits, and the vitreous turbidity cleared. The papillo-œdema subsided, and corrected vision again rose to $\frac{20}{15}$. In this condition the eye has remained after complete desensitization with lens protein and uveal pigment.

It is to be regretted that the clinical picture in this patient was so severe, that it did not permit desensitization with one protein, while the other was withheld. Thus it might have been determined if only one of the two proteins was responsible for the condition. Now it can only be said that either, or both, may have been concerned in the ocular reactions. This case appears to present rather dramatically the probability that after cataract operations, absorption of residual lens protein (or uveal pigment) may produce a definite and specific hypersensitivity, and a subsequent allergic reaction in the eye. Further investigation of the delayed uveal reactions following operation may show a similar situation.

Non-Specific Protein Therapy.

Non-specific protein therapy has been used in practically every inflammatory condition in the eye, including the

various conjunctivides, corneal inflammations, uveal inflammations, and the various trauma. The problems connected with the use of non-specific protein therapy in ophthalmology are in no way different from the problems connected with its use in inflammations occurring in other portions of the body. Therefore non-specific protein therapy had better be considered as a general problem and not as isolated ocular therapeusis.

The first observation on the effect of non-specific protein therapy was that of the Indian Plague Commission many years ago, who observed that anti-plague inoculations had a beneficial effect on miscellaneous infections, and drew attention to the therapeutic rôle which non-specific protein might play.

It was finally realized that any substance which would produce a general shock reaction often produced a therapeutic change. This reaction to non-specific protein which has been the subject of a great amount of study is characterized by the following phenomena:—chill, which follows the injection of the non-specific protein; fever, sometimes of 100–106 degrees, falling to normal within twenty-four hours; tachycardia, nervous irritability; glandular hyperactivity, accelerated nitrogen metabolism; increase, then a decrease in the permeability of the blood vessels; an increase in resistance to poisons; increase of lymph flow; leucocytosis, chiefly of the polymorphoneutrophiles, and more rarely of the eosinophiles; mobilization of the proteolytic enzymes and lipases; a decrease in the anti-ferment content of the serum; occasionally the mobilization of specific antibodies; and lastly the occurrence of a definite reaction around the focus of inflammation.

The focal inflammatory reaction is of special interest to ophthalmologists. It has been shown that every inflammatory focus will give a focal reaction after injection of a non-specific protein. Schmidt has shown that a non-tuberculous localized inflammatory process will react to an injection of tuberculin, and of other non-specific agents, nucleoproteins, nucleins, etc. Wolff-Eisner has recently stated that he believes this is due to a sensitivity against protein in general which is produced by a localized inflammatory focus. This focal reaction is definitely diphasic in character, characterized

in the primary phase by an increase in the inflammation, in the second phase by a decrease in the inflammation, and by healing.

It is not necessary to discuss the theories over the possible mechanism of non-specific protein therapy. Numerous such theories have been advanced. In general it appears that the beneficent effects of non-specific protein therapy are in the main dependent upon the stimulation of the fixed cells. Weichardt has been shown that while a small dose stimulates the cells, larger doses depress them.

Further study of the non-specific protein reaction has shown that there are an enormous number of substances which are capable, in a greater or lesser degree, of provoking the typical non-specific reaction. Among such substances are the counter irritants, the normal and immune serums, antitoxins, proteins, egg-albumin, milk derivatives, gelatin, nucleo-proteins, neucleo-hexyl, protein-split products, enzymes, tissue extracts, vaccines without number, bacterial extracts, colloidal metals, yeast, etc.

In the American Clinics we find three proteins commonly used in the non-specific protein reaction. The first of these is milk, or some of its derivatives. This is certainly the mildest. The reaction it produces is probably the most variable, as are likewise the therapeutic responses elicited. Evidence has been presented which indicates the reaction produced by milk is in proportion to its bacterial content.

Anti-diphtheritic serum is the second protein commonly used, and appears to be the general favorite. Its use has especially been urged by Key in hypopyon keratitis and other conditions, and recently it has been recommended by Verhof as almost a specific in sympathetic ophthalmia. When the sharp specificity of diphtheria antitoxins, and the concentrated refined serum now produced, are considered, it seems impossible to accord anti-diphtheritic serum any specific therapeutic action in inflammatory disease of the eye other than diphtheritic infections, or to regard the beneficent effects following its use as anything other than the results of non-specific protein therapy. The reaction following its use is usually sharper than the reaction following milk.

The third protein generally employed is bacterial vaccine,

usually typhoid vaccine. This may be given either subcutaneously or intravenously, preferably the latter. This protein has the advantage that the dosage may be more exactly controlled than with milk, and the response elicited prophesied with greater accuracy. The initial intravenous dose depends on the age and the condition of the patient, and the reaction desired. An average initial dose is about ten million bacteria. It should be repeated at about six day intervals and each dose increased from two to five million bacteria, according to the results desired, and already elicited. The therapeutic results obtained with this protein appear to be at least equal to those observed following other forms of non-specific protein therapy.

Our choice of proteins should not be limited to one protein. Nor should the non-specific protein reaction ever be used as a routine in any given type of case.

It has been emphasized that the reaction is essentially diphasic, the first phase being characterized by the rather violent general symptoms and by an increase in the local inflammation, and the second phase characterized by the definite beneficent effects and the resolution of the inflammatory process. Therefore no patient should be submitted to this reaction unless the patient is a good clinical risk, well able to stand the augmentation of disease incident to the first phase. Further, inasmuch as when all is said and done, the effects of non-specific therapy are in the main dependent upon the stimulation of the cells, such non-specific protein therapy should be used while the cells are still definitely capable of stimulation, and it must of necessity be of less value when the cells affected are exhausted by long drawn out disease. The question of dosage should be most carefully weighed for deaths from excess dosages have been reported by Eggerton, Krause and Mazza, Borral and other observers; also Weichardt has shown that while small doses stimulate the cells; larger doses depress the cells. In the event serums are used, the question of hypersensitivity to such serums should be carefully determined before the serum is injected into the patient. If the hypersensitivity is present, which can safely be determined by a preliminary skin test, the patient should be desensitized before the serum is administered.

In the case of vaccines, proteoses, and milk, the question of hypersensitivity is unimportant, but in the case of serums, there is a definite danger which should be guarded against. Diabetes, pregnancy, and alcoholism are also said to be contra-indications to the use of non-specific protein therapy.

While non-specific protein therapy is indeed one of the most valuable therapeutic weapons we have, it is nevertheless specialized therapy. The age and condition of the patient and the duration of the disease should be carefully considered before a protein is chosen. In the case of a debilitated patient, or when a mild reaction is desired, milk seems to be the protein of choice. In the event a more certain reaction is desired, anti-diphtheritic serum may well be used, after preliminary tests are made to determine the question of hypersensitivity. (If the local disease is advanced to considerable degree, a much sharper stimulus will probably be needed to evoke a response from a cell, fatigued by disease.) If the patient is a good clinical risk, killed bacilli may be used intravenously. But non-specific protein therapy should always be considered specialized, and never routine therapy, and no hard and fast rule be laid down. Our choice of protein and dosage should be governed by the reaction we desire to produce, and this should be controlled by the condition of the inflammatory lesion and the general condition of the patient.

CLOQUET'S CANAL VISIBLE IN THE LIVING, WITH OBSERVATIONS ON HEMORRHAGE INTO CLOQUET'S CANAL.

By Dr. OTTO BARKAN, San Francisco, Calif.

(With two drawings in the text.)

IN the following case, a cylindrical antero-posterior passage was ophthalmoscopically discernible, traversing the vitreous of each eye from the posterior surface of the lens to the optic disk. No vestige of fœtal elements could be discerned. The case therefore is not to be confused with those congenital anomalies of the vitreous described by various authors and classified by De Beck (1) as persistance of some portion of the fœtal hyaloid system in which organized remnants of hyaloid vessels, or their sheath, can be seen. In this case the canal was rendered visible solely by virtue of the contrast between its translucent contents and the turbid vitreous surrounding it.

Case Report.—G. V.—Male, age 65 years; in treatment at the Stanford Neurological Clinic for tabes. Gradual failure of vision since several years. Pupils—slightly irregular; 3*mm* wide equal; react sluggishly to light but normally to convergence; transillumination of the dilated pupil with the plane mirror shows a ring-shaped vitreous opacity which is symmetrically situated in both eyes, slightly nasal and just below the median axis; it undulates slightly on eye movements. Fundi show moderate neuritic optic atrophy and an old central choroiditis consisting of dot-like accumulations of pigment and small areas of rarefaction. Vision—$\frac{8}{10}$ each eye. Examination with the electric ophthalmoscope and suitable plus lenses shows a perfectly translucent cylindrical canal with a wide, funnel-shaped anterior end lying behind the posterior lens surface and running backwards to the lower portion of the optic disk. The average diameter of the canal is from one-third

to one-half disk diameter. When observed though the translucent contents of the canal, the disk appears bright and sharply defined in every detail but when viewed through any portion of the surrounding vitreous, it appears dull and slightly blurred. The canal seems to sag in its course, so that only the lower third to half of the disk can be seen through it. The surface of demarcation between the canal and the vitreous is transparent and is visible only by virtue of the optical properties which obtain at the surface of contact between two media of different refractive indices. The ring-shaped opacity of the vitreous which was seen by transillumination corresponds to a cross section of this cylindrical surface of demarcation. It is difficult to decide whether what appears to be the wall of the canal is thus merely an optical phenomenon or whether it consists of a transparent true, or false, membrane such as is the much discussed hyaloid. I was unable to detect any sign of such a membrane with the slit-lamp in the anterior portion of the canal.

The existence of the hyaloid or Cloquet's Canal is still a subject of controversy. Norris and Oliver (2) make the following general statement:—"Some observers have seen appearances in the vitreous which they have thought pointed to the existence of the hyaloid canal in which the artery lies, it and its cellular sheath having disappeared. It is usually believed that part of this canal exists in the normal eye (the Canal of Stilling) but that it is not visible with the ophthalmoscope. Alteration either in its contents or in its extent may possibly in some cases render it so."

My case seems to justify the presumption made in the last sentence.

In his monograph on "Anomalies of the Vitreous," De Beck has collected ten cases from the literature under the heading, "Persistence of the Canal of Cloquet." In most of these cases however the diameter of the Canal was no greater than that of a retinal artery or vein at the disk and its walls were grayish, semi-transparent. These cases would seem, in my opinion, therefore to be remnants of the vessel sheath rather than of Cloquet's canal and to belong to a group of cases of which one was recently reported by Scarlett (3) as "Opaque Canal of Cloquet with persistent Hyaloid Artery." This is the same type as that previously reported by Eason,(4) Giles (5),

Parsons, Shoemaker (6) and others, aptly termed by Hess as "Atypical embryonic development of mesoblastic tissue from which the vitreous is derived." These cases from their very nature do not concern us here. From a study of the cases of Manz, Holmes and Despagnet, De Beck comes to the conclusion that "In these cases, there remains, as a vestige of the hyaloid system, a delicate, nearly transparent tubular sheath, passing through the center of the vitreous from the disk to the lens. This is regarded by some as the persistence of the delicate membranous lining of the Canal of Cloquet through which the hyaloid artery runs and by others as the remains of the outer sheath of the vessel itself. This difference of opinion is due to our lack of decisive knowledge of this canal, either in the embryo or adult. According to Stilling, a sheath involving the hyaloid artery remains as an open tubular canal after the vessel has disappeared. Manz and other authors hold this view while Carrerras and others hold that there is no real, separate and distinct Canal of Cloquet. The former view is most probably the correct one. Anatomical examinations as well as ophthalmoscopic studies show that this canal consists of a delicate and nearly transparent membranous tube. It is much wider than the vessel ever is, being usually one and a half millimeters or more in diameter in its narrowest part—that is, about as wide as the disk itself. It usually terminates at either extremity in an even wider funnel-shaped expansion than this, so that the disk is usually well covered at the posterior end of the canal. This condition is however not always present; sometimes the sheath fades away towards the disk and runs out into a pointed extremity which fixes it at this point; even this may fade away so as not to be visible ophthalmoscopically. . . . There is little doubt but that in some instances at least this canal remains patent during adult life."

E. Fuchs (7) assumed the persistence of Cloquet's Canal in the adult on the basis of observations in pathological conditions; in cases of traumatic iritis he observed papillitis while the surrounding retina was normal. Similarly in cases of abscess formation in the anterior portion of the vitreous, anatomical examination showed a strand of pus cells extending backward from the center of the vitreous to the disk. These

observations strongly suggested an axial lymph-stream, carrying, in the first instance, toxins, and in the second, pus cells in an antero-posterior direction. Further, in two cases of hemorrhage into the vitreous, anatomical examination showed a cylindrical column of blood corpuscles extending to the optic disk from a blood-clot lying behind the lens. The walls of this cylinder or canal were lined with corpuscles. Berger had also observed with the microscope the Canal of Cloquet filled with sanguino-purulent exudate extending from the posterior lental space to the disk. Strong positive evidence was further furnished by Bribach who removed the vitreous from the pig's eye in toto and succeeded by means of stereoscopic photographs in demonstrating a canal extending from the disk about two-thirds of the way forward through the vitreous, thereby confirming Stilling's previous experiments.

On the other hand, the existence of the canal in the adult has been denied in recent years by such authorities as Wolfrum (9) who believes the canal observed by Bribach and Stilling to be an artefect. Recently both Koeppe and Vogt, working with the slit-lamp, have not only failed to find a trace of the canal in the adult but also adduce evidence to the contrary. Koeppe states: "The normal vitreous does not contain in its anterior half a trace of Cloquet's Canal or remnants thereof." Vogt, after having observed an optically empty posterior lental space, later when using the microarc slit-lamp, states that "No vitreous is free of frame work, not even in the axial area."

My case then appears to show a true Canal of Cloquet. The case proves, if further proof is necessary, that the canal may persist in the adult vitreous. On the basis of the following observations on hemorrhage into the axial area of the vitreous, one is led to believe with Bribach and others that a central canal or at least a marked difference in structure of the axial area which functions as a canal and approximates a canal in structure exists in at least a fair percentage of normal adults.

Hemorrhage Into Cloquet's Canal.

Hemorrhage into Cloquet's Canal has, to my knowledge, never been reported as a clinical entity. As mentioned above,

Fuchs examined two cases of vitreous hemorrhage anatomically and Berger one; both found a cylinder of blood running through the vitreous from lens to disk. Since my attention was first called clinically to two such cases by the late C. v. Hess, who termed them "Hemorrhage into Cloquet's Canal," I have observed a surprisingly large number of them. Typical ones show a massive hemorrhage extending from the region of the disk along the antero-posterior axis of the vitreous, sharply delimited and of columnar or digitate shape. That such marked cases have been but rarely observed is, I believe, due to the very size of the hemorrhage, for the more massive the latter the less apt it is to be confined to Cloquet's Canal and the more likelihood is there of its breaking through into the vitreous. On the other hand, the smaller hemorrhages, which I have found to be frequent, easily escape observation for the following reasons: They are very rapidly absorbed, much more so it would seem than are hemorrhages into the body of the vitreous. (This may well be explained by the presence of an axial lymph stream in the canal.) They more often occur in old people in whom opacities of the vitreous already exist or they occur simultaneously with other hemorrhages in the body of the vitreous from which they cannot be distinguished. Furthermore they cannot occur in cases of prëexisting vitreous opacities in which the vitreous has become liquefied and Cloquet's Canal is therewith non-existent.

The following case serves as a typical example of a small hemorrhage into Cloquet's Canal:

Case I.—Mr. B.—Age 65, consulted me in Sept., 1921. For two years, he had noticed spots floating in front of his right eye; their sudden appearance had been ushered in by flashes of light. There were several vitreous opacities of moderate size in the right eye. The vitreous of the left eye observed under mydriasis was clear. Retinal vessels of both eyes showed moderate sclerosis. In 1922, patient saw flashes of color in front of the left eye and described the attack as being similar to the one he had had in the right eye three years before. Since then, he had been troubled by a dark shadow near the center of fixation. Thirty-six hours after the attack, a translucent, gelatinous vitreous opacity could be made out in the median axis. It was joined to the disk by a very slender pedicle and moved but slightly with

movements of the eye. The patient stated that in the course of several weeks, the shadow did not change in size but became less intense until it finally disappeared. It retained its position in the axial area throughout.

CASE II.—Mr. K., age 37. Seen 2/3/23. Sudden pain in right eye and slightly blurred vision followed cough of two weeks' duration. Right eye—Fundus shows small hemorrhage of retinal artery at upper border of disk. (a) From this point, the blood trickles down to form a typical half-moon shaped pre-retinal hemorrhage, (b) 1 P. D. below disk and 5. P. D. in width. From this lake of blood, a very faint film of blood (c) extended over the retina downwards and anteriorly until it was lost from view anterior to the equator. In the axial area of the vitreous, a central canal, with funnel-shaped anterior end (d) gradually tapering to a filament towards the disk, could be discerned by carefully focussing with the direct method. The transparent walls of the canal had been rendered visible by a lining of a thin film of blood. The vitreous of the left eye was normal.

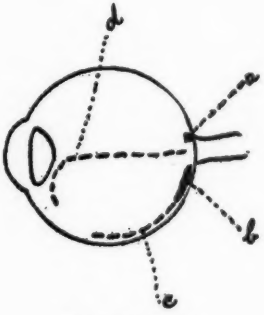

DIAGRAM NO. I

DIAGRAM NO. II

Diagram I.—Shows the canal in profile. It is impracticable to represent the appearance in any other way.

Diagram II.—Shows in a frontal view, the striate distribution of the blood film at the anterior funnel-shaped end of the canal behind the posterior lens surface. It is impossible to determine whether the blood had entered the canal at its narrow end at the disk and had proceeded anteriorly to be poured out of the anterior funnel-shaped end as in Diagram II

or whether the blood which had trickled down and forward from the pre-retinal lake of blood in Diagram I had been carried further on to and into the anterior funnel-shaped end by the lymph-stream. The fact that I was unable to discern any connection ophthalmoscopically between the filamentous end of the canal and the disk or its neighborhood suggests that the latter view is the correct one.

In none of the three reported cases, were there any congenital abnormalities present.

Conclusions. (1).—Cloquet's Canal may occur and may be seen ophthalmoscopically under certain favorable conditions in the normal adult vitreous. The canal would seem to be more frequently present in the adult than heretofore supposed. (2).—Hemorrhages confined to the axial area of the vitreous are not uncommon. They may be regarded as a clinical entity and aptly termed "Hermorrhages into Cloquet's Canal." (3).—Supports the view that an antero-posterior lymph-stream exists in the axial area of the vitreous.

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THE RÔLE OF THE ARSPHENAMINES IN THE PRODUCTION OF OCULAR LESIONS.

By Dr. E. L. Zimmermann, Baltimore.

Syphilologist to the Baltimore Eye, Ear and Throat Charity Hospital and the Presbyterian Eye, Ear and Throat Charity Hospital.

In the treatment of ocular syphilis the arsphenamines have partially fulfilled early expectations. In uveitis and optic neuritis results are in general gratifying. In tabetic optic atrophy and in interstitial keratitis, however, the response is disappointing.

The syphilologist is apt to focus attention upon eradication of the infection. The ophthalmologist on the other hand is primarily interested in preservation and restoration of vision. In the treatment of ocular syphilis the following dicta are to be emphasized. Antisyphilitics, especially at the commencement of their administration, should be so regulated as to eliminate the possible development of a deleterious Jarisch-Herxheimer reaction. Secondly, when treatment threatens to produce further impairment of vision, as in certain types of tabetic optic atrophy, antisyphilitics should be cautiously administered or even omitted.

Following the administration of the arsphenamines there may occur three types of ocular reactions, the mechanism of each of which is essentially different. Those attributable to a direct toxic action of the drugs on the normal eye are uncommon and usually of little consequence. The more frequent and more serious reactions depend upon the existence of actual syphilitic changes in the eye and occur in the form of Jarisch-Herxheimer reactions and of oculorecurrences (iridorecurrences and ocular manifestations of neurorecurrences).

I. True Toxic Reactions.

These may originate in an apparently normal eye or in connection with ocular lesions other than syphilitic.

Conjunctival Hyperæmia.—Conjunctival hyperæmia, at times associated with marked palpebral œdema is common in nitritoid reactions following arsphenamine and may be dismissed as part of a generalized peripheral vasodilatation.

However it may occur as an isolated phenomenon. Milian (1) in 1911 called attention to this type of reaction. The vasodilatation of the conjunctival vessels is usually bilateral and symmetrical involving the lower and outer portions of the bulb without affecting the upper half. Even when diffuse the lower and outer portions are most intensely injected. According to Milian this conjunctival reaction is significant in that it presages symptoms of arsenical intolerance of more serious import.

Conjunctival hyperæmia also occurs in connection with so-called fixed arsphenamine rashes. This term designates a type of eruption similar to antipyrin and phenolphthalein rashes, in which erythematous or urticarial lesions with or without subsequent pigmentation tend to recur after each injection of arsphenamine with precisely identical localization.

Such a reaction was first described by Naegeli (2). In his patient it is remarkable that the areas most sensitive to the drug were the left bulbar and palpebral conjunctiva and the skin of the cheek and forehead, especially in the region of a small pigmented nævus. At times the conjunctiva of the left eye became chemotic a few minutes after the injection, that of the right eye remained normal or reacted to a much less degree.

Kraus' (3) patient, asymptomatic except for a positive Wassermann, had already complained of itching of the eyelids following injections of neoarsphenamine. On resuming treatment there occurred after each dose of the drug unusual vasomotor manifestations. About a half minute after the injection there developed a slight burning sensation of the palpebral borders, which gradually became intensified. The conjunctivas, especially in the region of the caruncle and the plica semilunaris became congested. In about ten minutes the congestion commenced to abate. Concomitant with the

ocular lesions there occurred each time in exactly the same locations, in the left supraclavicular and in the right malar regions, erythematous patches, one with a central wheal.

D. Fuchs (4) observed the recurrence of conjunctival hyperæmia in the right eye following each injection of neoarsphenamine. There were no associated cutaneous lesions nor any other toxic manifestations. It seems reasonable to interpret this phenomenon as analagous to fixed arsphenamine rashes.

The following reaction, unique in the writer's experience, belongs to this type of reaction.

J. P., a white male, 26 years of age, had received two intravenous injections of arsphenamine for early secondary syphilis. After a lapse of six weeks from treatment severe headaches and malaise set in. The only positive findings on physical examination were polyadenitis and a large immobile left pupil. Ophthalmoscopy, normal fundi.

Laboratory data.	
Blood Wassermann.	Positive.
Spinal fluid.	
Pleocytosis.	512 cells.
Pandy.	Heavy cloud.
Fixation with 0.1 cc. of fluid.	
Lange colloidal gold.	Paretic curve.

The initial injection of 0.3 g. of neoarsphenamine was well tolerated and relieved the headache considerably. Immediately after the second injection of 0.45 g., the patient experienced an itching of the right eye of only a few moments duration with a hyperæmia limited to the conjunctiva of that eye. A third injection of 0.6 g., however, resulted in congestion of the conjunctivas of both eyes, much more marked in the right, and the appearance of a few urticarial lesions on the flexor surface of both forearms. In spite of a preliminary injection of adrenalin, there was a recurrence of the conjunctival hyperæmia and in addition pronounced œdema of the lids and lips. Subsequent injections of silverarsphenamine were tolerated without untoward symptoms.

Transient Myopia.—A curious reaction has been recorded by Dupuy-Dutemps and Perin (5) and by Milian (6) in the

form of transient myopia, resulting probably from spasm of the ciliary muscle without involvement of the sphincter. The exact etiology of this phenomenon is at present uncertain.

Retinal Hemorrhages. Vitreous Hemorrhages.—In contrast to the vasomotor reactions involving the conjunctiva, another group of lesions affecting the posterior structures of the bulb are of grave significance.

Krückmann (7) has several times observed retinal hemorrhages following arsphenamine. For the most part the hemorrhages occurred after the second and third injections. In each case the patients were of advanced age and were asymptomatic except for a positive Wassermann. Several gave evidence of renal disease associated with hypertension. Krückmann warns against large doses of arsphenamine in patients over fifty, especially with impairment of renal function.

Audry (8) reports the occurrence of vitreous hemorrhages in a tabetic subsequent to an injection of neoarsphenamine.

In a patient with an uncertain diagnosis of syphilis (Wassermann negative) Horvath (9) observed repeated retinal hemorrhages after a fourth injection of arsphenamine (g. 0.9!).

Chorioretinitis. Neuroretinitis.—Another group of reactions supposedly due to arsphenamine reactions are heterogeneous in character and their etiology will be further discussed after summarizing the reports.

Harding (10). A twenty-four year old male with an initial lesion was treated with arsphenamine (0.4–0.6g.) in courses of six to eight injections. After the fourteenth injection vision began to decline. Following the seventeenth injection vision has been reduced to O.D. $\frac{5}{15}$, O S. $\frac{1}{10}$. The right fundus was obscured by a hazy vitreous. The left fundus was only seen in spots, the papilla not being observed. Under atropine alone vision improved to $\frac{6}{15}$ and $\frac{8}{10}$. A month later an eighteenth and a nineteenth injection were administered. Again there was a marked decrease in vision with increased vitreous opacities. After a lapse of one month mercurial inhalations were instituted and produced remarkable improvement in the ocular condition. Vision improved to $\frac{6}{6}$ and $\frac{8}{8}$ in the right and left eyes respectively, the vitreous became perfectly clear, the disks appeared somewhat pale.

Oden and White (11).—In a patient treated for primary syphilis an optic neuritis developed after the fifth injection of arsphenamine. Twelve hours after the injection vision became blurred in the right eye. Ocular examination: O.S. Vision and fundus normal. O.D. V. $\frac{20}{200}$. Ophthalmoscopy. Disk elevated to the extent of four diopters, clouding of the surrounding retina, arteries narrowed, veins distended and tortuous. Perimetry. Central scotoma for red and green.

Gregario (12).—In three young adults who had been infected three, five and twelve months previously, there developed during a course of arsphenamine after the second, third and fifth injections, respectively, a neuroretinitis with vitreous opacities. The response of the lesions to treatment was unsatisfactory and in each patient a postneuritic atrophy resulted.

Finnoff (13).—Development of a bilateral neuroretinitis in a patient with secondary syphilis while under arsphenamine and mercurial inunctions.

In analysing this group of lesions involving the posterior ocular structures, it seems reasonable to exclude a genuine toxic reaction. The retinal hemorrhages are presumably dependent upon retinal changes due to cardiovascular disease. The observation of Harding as well as that of Oden and White are probably to be considered as an aggravation of syphilitic lesions during arsphenamine treatment. This paradoxical phenomenon of intensification of lesions during a course of intensive treatment has been observed in other organs than the eye, especially in the central nervous system. In Harding's patient the subsequent rapid response to mercurial inhalations indicates the syphilitic character of the lesion. In Oden and White's observation the monocular occurrence of the optic neuritis militates against its interpretation as a true toxic reaction. Analysis of the spinal fluid would have helped to solve the etiology of this unusual lesion.

Corneal Necrosis.—An unique lesion involving the cornea has been recorded by Hegner (14). A male with neurosyphilis (myosis with sluggish reaction to light, hyperactive reflexes, positive Babinski) developed a diffuse erythema following a second injection of neoarsphenamine. The third injection resulted in a severe exfoliative dermatitis and exitus. Associated with the dermatitis there occurred an unusual ocular

change commencing as a croupous conjunctivitis followed by clouding of the lower half of the cornea which eventually became diffuse. Subsequently the cornea underwent necrosis and perforated. Microscopic examination showed a panophthalmia. Streptococci were demonstrated in the tissues. The question arises whether there was an actual toxic degeneration of the cornea with subsequent secondary infection or whether the corneal lesion was not entirely dependent upon a pyogenic infection, so commonly complicating the grave exfoliative dermatitides resulting from the administration of the arsphenamines.

In summarizing it may be stated that according to the present status of knowledge the only true toxic arsphenamine reactions involving the normal eye occur in the form of conjunctival hyperæmia. There is evidence that it may further damage retinal vessels already involved by cardiovascular and renal disease. However there is no data, clinical or experimental, to indicate that a normal retina or optic nerve are ever affected by the administration of arsphenamine or of neoarsphenamine.

II. Ocular Jarisch-Herxheimer Reactions.

Serious consequences may arise, however, from the action of arsphenamine on an extensively diseased eye in the form of Jarisch-Herxheimer reaction. Whether the latter results from a sudden destruction of masses of spirochetes with liberation of toxins or from a temporary increase in activity of the organisms preceding their destruction is problematical. As is true in syphilitic processes in general, so in ocular syphilis a Jarisch-Herxheimer reaction may manifest itself as an intensification of an active lesion, as an activation of a quiescent lesion, or as the unexpected appearance of changes in structures previously presenting no clinical evidence of any pathological process.

Uveitis.

In syphilis involving the anterior uvea all three types have been observed. Intensification of an acute iridocyclitis is frequent. At times for twenty-four hours following an injection of arsphenamine subjective symptoms become aggravated and there is an increase in vascular reaction. This intensi-

fication may assume an unusual degree as in a case recorded by Flemming (15). Injection of 0.5 g. of arsphenamine resulted in a marked exacerbation of an already acute iritis with the production of hyphæma and an increase in the number of deposits on Descemet's membrane.

Gallemaerts and Kleefeld (16) in their studies with the slit lamp noted the appearance of abundant deposits on Descemet's membrane following the injection of 0.12 g. of sulfarsenol. Previous to treatment there had been present an acute iritis but without involvement of the posterior surface of the cornea.

The second type, activation of an old quiescent uveitis as a result of injections of arsphenamine, is rare. In fifteen patients with an old syphilitic uveitis, mostly negroes with neglected lesions presenting such manifestations as extensive synechiæ, choroidal atrophy and complicated cataract, untreated for syphilis except for nostrums, the writer observed in no instance any sign of uveal irritation following the administration of arsphenamine.

A few instances of a quiescent iritis becoming active as a result of arsphenamine occur in the literature. This phenomenon is apparently uncommon. Toulant (17) reported such a reaction. Terlinck (18) observed two analagous reactions following mercury. One patient, who had suffered two attacks of acute syphilitic iritis in the left eye and had been treated according to the chronic intermittent method, developed a recurrence of iritis following a third injection of enesol, after the fourth hyphæma and secondary glaucoma. Under arsphenamine the lesion cleared up promptly.

The third type, in which an iridocyclitis develops in an eye clinically normal, is also uncommon. Terlinck cites a patient with a neurorecurrence (bilateral optic neuritis) who developed an acute iritis three days after an injection of arsphenamine.

A Herxheimer reaction involving the uvea may manifest itself by extension of an active process to tissues previously uninvolved. Such a case has already been recorded (19). A patient, who had been observed twenty-two years previously with a bilateral optic neuritis of syphilitic origin, which had responded to mercurial treatment with a good functional

result, developed after a long period of freedom from symptoms, an acute choriorentinitis in the right eye. The blood Wassermann was positive. On the day following the second injection of arsphenamin (g. 0.15–0.30) a violent iritis with hypopyon developed in the right eye. However following the third injection of g. 0.6 the exudate underwent absorption and the iritis subsided rapidly. The smaller initial dose served to stimulate clinically inactive foci of spirochetes in the anterior uveal tract, a reaction which was promptly inhibited by the subsequent larger dose.

An ocular Jarisch-Herxheimer reaction observed by Igersheimer (20) is noteworthy as exemplifying as in the patient just mentioned that the distribution of organisms in ocular tissues may be much more extensive than indicated by clinical appearances. A patient with an iritis papulosa of the right eye developed a marked papilloretinitis in the left apparently normal eye two days after an injection of arsphenamine. Igersheimer interprets this reaction as indicating an activation of spirochetes in a retina previously showing no ophthalmoscopic changes.

Terrien and Prelat (21) record the case of a male with primary syphilis who had been treated for one year with protoiodide and intramuscular mercury. At the end of this period an acute iritis developed in the left eye. Two days after a second injection of arsphenamine (g. 0.4.) not only was there an aggravation of the iritis but there developed a papilloretinitis.

Stoewer (22) observed the development of a violent iritis with considerable exudate into the aqueous a few days after a dose of arsphenamine. Previous to treatment there had been present a syphiloma involving chiefly the papilla, but clinically the anterior uvea was entirely free of pathological changes.

Choroid.—Von Greef (23) noted the production of a distinct areola of hyperæmia around the individual lesions of a choroiditis as a result of an injection of arsphenamine. Such an observation is unique.

Keratitis.—Herxheimer reactions in interstitial keratitis of congenital syphilis are rare. The lesion runs its course in spite of intensive treatment and when monocular at the commencement of treatment, in the majority of instances the

second eye eventually becomes involved. There is seldom a sharp therapeutic response as in uveitis and accordingly it is only to be expected that the initial intensification so common in iridocyclitis should be absent.

A girl, aged nine, congenitally syphilitic, observed by Lacombe (24), asymptomatic except for a positive Wassermann, received between October 2 and 20, six injections of an arsenical (aminoarsenophenol de Pomaret). On the twenty-third of October an interstitial keratitis developed in the left eye, subsequently involving the right also. It is questionable whether the interstitial keratitis was actually incited by the drug or whether its occurrence subsequent to treatment was a mere coincidence and illustrates the impotency of a course of treatment to prevent an interstitial keratitis on the verge of developing.

In a considerable number of congenitally syphilitic children with lesions other than interstitial keratitis under the writer's observation, in no instance has a corneal lesion developed shortly after the administration of arsphenamine.

In a patient with keratitis pustuliformis profunda dependent upon acquired syphilis observed by Arne Bryn (25) a dose of arsphenamine was followed by increase of the hypopyon from a depth of one *mm* to half fill the anterior chamber. The second dose gave rise to further increase in the exudate to be followed by progressive improvement of the corneal lesion with disappearance of the hypopyon.

Optic Neuritis.—Herxheimer reactions in uveal syphilis seldom cause any permanent injury to ocular function. However in optic neuritis the danger is more real and the possibility of the occurrence of such an injurious reaction necessitates caution in treatment.

Julius Hirschberg (26) reports the occurrence of sudden blindness following an injection of arsphenamine in a patient with optic neuritis. Under mercury vision improved until it reached its previous acuity.

In Brüning's (27) patient, infected extragenitally, an optic neuritis developed five days after a 0.4 g. dose of arsphenamine. No mention is made of ophthalmoscopic findings previous to the injection.

An outspoken Jarisch-Herxheimer reaction occurred in a

patient at the Baltimore Eye, Ear and Throat Hospital Dispensary. A negro with early secondary syphilis received six weekly injections of arsphenamine at a government clinic. Eight weeks after the last injection failing vision and excruciating headaches set in. Examination showed evidence of a typical neurorecurrence. Ocular examination by Dr. M. Randolf Kahn: V. O. D. et O.S. $\frac{20}{200}$. Ophthalmoscopy. Papillitis with an elevation in each eye approximating seven diopters, distension and tortuosity of the retinal veins, marked narrowing of the arteries. The blood Wassermann was negative with all antigens with water-bath and ice-box fixation. Spinal fluid: pleocytosis (420 cells, chiefly lymphocytes, per *cmm*), Pandy strongly positive, fixation with 0.1 *cc* of spinal fluid, and a luetic zone Lange curve. Two days after an injection of neoarsphenamine (g.0.6) he returned with a further marked reduction in vision (hand movements) and a striking change in the fundal picture. In each eye there were now present numerous peripapillary hemorrhages, for the most part along the veins as they entered the obscure margins of the elevated nervehead.

The prophylaxis of such disastrous reactions is obvious. In all optic neuritides antisyphilitic treatment should be instituted with caution. Either a preliminary course of mercury or bismuth should be administered or if arsphenamine is employed from the very outset the initial dose should be small.

Tabetic Optic Atrophy.—As in optic neuritis Jarisch-Herxheimer reactions may produce disastrous results in tabetic optic atrophy.

Visual disturbances occur at times in the form of flashes of light during the twenty-four hours following an injection. Transitory reactions have been observed by Jansen (28) and Spiethoff (29). In Jansen's patient with incipient tabes dorsalis but without definite ophthalmoscopic evidence of degeneration visual disturbances set in four hours after an injection of arsphenamine and after persisting two hours cleared up completely. The possibility offers itself that the visual disturbances were caused by irritation of the optic nerve early in the course of the disease before appreciable clinical changes had developed. Spiethoff reports the sudden loss of sight in a

tabetic fifteen hours after an injection of arsphenamine persisting for several minutes.

Sheehan (30) observed a patient with primary optic atrophy and symptoms of spinal cord involvement in whom vision was seriously affected by a course of Swift-Ellis treatments. Following the initial injection a vision approaching normal commenced to fail and by the end of six weeks the patient was practically amaurotic.

Behr (31, 32, 33) has differentiated a type of tabetic optic atrophy characterized by marked subjective symptoms in the form of flashes of light and by a disk with changes indicating a far advanced atrophy, in which intravenous arsphenamine results in rapid diminution of vision. He ascribes the deleterious affect to a Jarisch-Herxheimer reaction. What small amount of the drug penetrates the pial membrane to reach the nerve tissue proper merely serves to stimulate the spirochetes and aggravate the lesion.

In a previous report (34) on the result of treatment of tabetic optic atrophy, a type of lesion was differentiated characterized by a maximum contraction of white and color fields, at times within ten degrees and a central vision approaching normal, in which the liability of serious damage as a result of intensive treatment was emphasized. One striking case was cited in which decline in vision became fulminating during a course of Swift-Ellis treatments. After each injection the patient complained of outspoken subjective symptoms in the form of flashes of light to be followed by a considerable decrease in vision which remained permanent. In such atrophies there is a relatively small part of the nerve remaining functional. A slight reaction is enough to impair irretrievably this portion already affected to some extent by the disease. It was pointed out that in this type of tabetic atrophy it is better to eliminate intensive treatment than to risk hastening the onset of amaurosis. That such an effect is not inevitable is demonstrated by the experience of Schacherl (35) with a patient presenting a tabetic optic atrophy with functional defects of this character who maintained a vision of $\frac{18}{18}$ during an entire year of intraspinal treatment (addition of one *mg* of neoarsphenamine to the patient's spinal fluid). It is a recognized fact in syphilitic processes in general that the

intensity of the Jarisch-Herxheimer reaction cannot be predicted. It may be pronounced or it may be absent. Accordingly one would expect a variation in degree of reaction in tabetic optic atrophy, which would explain the lack of uniformity of response of this lesion to treatment.

Ophthalmoplegias.—A Herxheimer reaction rarely manifests itself as an ocular paralysis. An unusual reaction involving only the ciliary muscle is reported by Makrocki (36). Six days after an intravenous injection of arsphenamine and two days after an intragluteal one, there developed a bilateral paralysis of accommodation gradually becoming complete. In four weeks accommodation had become normal again. Possibly this reaction is analagous to the transient myopia previously described. In the one there is an irritative lesion of the nerve resulting in spasm of the ciliary muscle, in the other a loss of function of the nerve with paralysis.

III. Neurorecurrences and Iridorecurrences.

Ocular Lesions following Insufficient Treatment of Primary or Secondary Syphilis with the Arsphenamines.

The third type of ocular reaction attributable to the administration of the arsphenamines is really an expression of the effective spirochetocidal action of the drugs. Their brusque and incisive therapeutic action in primary and secondary syphilis, a period in the disease at which the spirochetes are exposed to the drug in contrast to the more protected localization of the organisms in tertiary syphilis when fixed tissue changes predominate, causes a rapid and massive destruction of spirochetes. In this way are inhibited certain protective mechanisms which develop when the disease is allowed to progress without therapeutic interference or under the less drastic mercurials. The surviving organisms in resuming activity encounter a defenseless host and the resulting reaction is a marked one. Two organs are especially prone to suffer, the central nervous system and the uvea. Involvement of the former results in the production of a neurorecurrence (neurorezidiv) and manifests itself in the ocular structures as an optic neuritis or paralysis of the internal or external ocular muscles. When the uvea is affected a so-called iridore-

currence (iridorezidiv) results. This designation is in the true sense of the word unsuitable in as much as the lesion is seldom limited to the anterior uvea nor indeed to the uveal tract. The lesion at times manifests itself as a panophthalmia.

Ocular Manifestations of Neurorecurrences.—By referring to the appended table, it will be seen that cochlear and vestibular changes predominate. However ocular lesions are very frequent in neurorecurrences, which often manifest themselves as an acute syphilitic meningitis with polyneuritis of the cranial nerves. In a total of 256 neurorecurrences analyzed in the table in 99 there was involvement of one or more of the following cranial nerves, optic, oculomotor, abducens or trochlear.

Optic neuritis may cause no subjective symptoms and only be detected on routine examination of the fundus. It may vary clinically from a hyperæmia of the papilla to a papillitis with an elevation of several diopters. The latter extreme type is often associated with perpipapillary hemorrhages. An excellent illustration of this condition may be found in Igersheimer's monograph, *Syphilis und Auge* (37). According to Gennerich (38) central scotomas are frequently present and ophthalmoscopic examination shows for the most part circumscribed retinal hemorrhages. In one of his patients there was associated with the optic neuritis an extensive retinal arteritis with thrombosis of the superior retinal artery.

Pathological studies of neurorecurrences with papillitis determined ophthalmoscopically previous to death have been made by A. Fuchs (39), Pirilä (40), Lloyd (41), Nonne (42) and Pette (43). In only one report is any special consideration given to the optic tract. A patient observed by A. Fuchs developed subsequent to a course of mercury and neoarsphenamine for secondary syphilis a marked papillitis without functional defects, a right abducens and a left facial paralysis. The spinal fluid showed pronounced abnormalities, the blood Wassermann was negative. Following nineteen injections of silverarsphenamine fatal toxic symptoms set in. Postmortem examination showed acute yellow atrophy of the liver. Unfortunately pathological examination of the ocular structures was fragmentary and limited to one centimeter of the left optic nerve and to the same length of the right nerve and to the right bulb. The right papilla was found to be entirely normal.

In either optic nerve the only pathological findings consisted of a slight lymphocytic infiltration and in places considerable glia proliferation in the peripheral portions of the nerve. The pia seemed uninvolved. The intensive treatment immediately following the appearance of the optic neuritis may have obscured the original pathological picture. For this reason a definite interpretation of the genesis of the lesion is uncertain. It may well have had a meningeal origin. Absence of infiltration in the pia may be accounted for on the same basis as the negative findings in the papilla, which had been definitely involved clinically previous to treatment.

It is plausible that papillitis may have two distinct origins in neurorecurrences, one originating from primary involvement of the meninges with extension to the optic nerve, the other developing from a lesion of the nerve itself. There is evidence to support such a supposition in as much as papillitis may occur as a recurrence following insufficient arsphenamine in early secondary syphilis without any clinical signs of neurosyphilis and with a normal spinal fluid (cytology, globulin content, Wassermann titrated to *2cc*, negative colloidal curves).

Ocular Paralysis.—As in neurosyphilis in general the oculomotor nerve is most frequently involved and the trochlear infrequently. Only the internal ocular muscles may be affected. In the patient previously cited in connection with conjunctival hyperæmia following arsphenamine, acute syphilitic meningitis was associated with an oculomotor paralysis involving only the sphincter pupillæ.

Iridorecurrences.—As previously stated this designation is misleading in as much as it fails to indicate the extensiveness of the lesion. In its biological significance it corresponds exactly to the neurorecurrence. In fact reference to a group of thirty-four neurorecurrences previously analyzed from material of the Johns Hopkins Hospital Dispensary (44), shows that there was an actual association of acute uveitis and acute syphilitic meningitis in two. In the extensive series of Benario (45) there was a similar symptom complex in two. Henser (46) observed an association of acute iritis and a neurorecurrence with epileptiform attacks. Rochon-Duvigneaud and Monbrun (47) cite two instances of an associated acute iritis

and neurorecurrence, each with papillitis or papilloretinitis and spinal fluid abnormalities.

The findings of Brown and Pearce (48, 49) in rabbit syphilis suggest a plausible explanation of the genesis of these lesions. These investigators found that in rabbit syphilis produced by a constant strain of spirochete pallida there occurred an appreciable connection between experimental conditions employed and the resulting type of disease. Certain tissues tended to become involved in a given order with iritis tending to occur toward the end of the cycle of tissue involvement. By diminishing or suppressing the primary lesion, either by excision of the chancre or by the administration of subcurative doses of arsphenamine it was possible to modify the course of the disease by conferring protection to certain tissues, protection however failing to reach the eyes, the lesions of the cornea occurring as the only manifestations of generalized infection. In fact conditions which were unfavorable for other lesions of generalization tended to reduce the relative incidence of eye lesions. In the development of iridorecurrences in human syphilis there is the same suppression of primary or secondary syphilis with subsequent occurrence of uveitis as an isolated manifestation of recurrence or at times associated with syphilitic meningitis.

As to the relative frequency of neurorecurrences and iridorecurrences, there occur in the writer's material forty-four instances of the former and sixteen of the latter, a ratio which may not represent the actual preponderance of neurorecurrences. Patients with acute uveitis would be likely to attend an eye, ear and throat clinic even when arsphenamine had been administered previously in some other institution. Among the neurorecurrences only patients with optic neuritis with marked visual disturbances, extraocular paralysis or with cochlear symptoms would attend such a clinic, and even then the focal lesions are so overshadowed by the general symptoms of acute syphilitic meningitis that patients go elsewhere.

The statistics of Oscar Fehr (50) (51) are instructive in that they are derived from the first year or two following the introduction of arsphenamine when hope for a cure of early syphilis by a single massive dose of the drug was entertained. Among three hundred and forty patients with early syphilis with

normal ocular findings previous to treatment, three hundred and six developed no clinical recurrence during the period of observation. Among the thirty-two developing manifestations of ocular recurrence, there were twelve with iritis, three with chorioretinitis, eleven with optic neuritis and six with ocular palsies. Of the twelve iritides which developed two to twelve weeks after injection, nine were acute forms with changes pathognomonic of syphilis (five with iritis papulosa), three were mild indifferent types. Of three with chorioretinitis one was of a severe hemorrhagic type. Fehr emphasizes the fact that these uveal lesions occur uniformly in patients treated for early syphilis.

These ocular reactions are characterized by their acuteness, extensiveness and by the frequent occurrence of syphilomas. Bray (52) described an iritis papulosa developing in the left eye six weeks after the administration of a dose of arsphenamine to a patient with secondary syphilis. Bahr (53) observed a "gumma" of the iris develop five weeks after a dose of arsphenamine. Kumagai's (54) patient had received a subcutaneous injection of arsphenamine for primary syphilis. Six weeks later vision became blurred and diminished rapidly. On ocular examination the left eye was found to be normal. External examination of the right eye was also negative. Ophthalmoscopy showed fine vitreous opacities, which however did not obscure the fundus to any degree. The papilla was replaced by a greyish-white mass projecting almost eight diopters into the vitreous. The surrounding retina was hazy and there were numerous peripapillary hemorrhages. The veins were dilated and the arteries narrowed or invisible. The visual field was contracted concentrically. Kumagai considers the process in no way an expression of neurosyphilis, but entirely an intraocular process consisting of a syphiloma of the papilla.

A similar ocular reaction is recorded by Stoewer (22). A patient originally receiving two injections of arsphenamine for secondary syphilis complained two months later of diminished vision in the left eye. External examination was negative. The whole fundus was whitish in appearance and the vessels could not be distinguished. A few days after a dose of arsphenamine there set in a violent iritis with considerable

exudate, which obscured the fundus for an extended period. (Jarisch-Herxheimer reaction.) Several weeks later there could be distinguished in the region of the papilla a whitish tumor encroaching for some distance upon the surrounding retina and a few retinal hemorrhages. As in Kumagai's observation the lesion is considered as a massive syphiloma involving chiefly the papilla.

Of special interest are the instances in which the ocular reaction was so severe and the response to antisyphilitics so unsatisfactory that enucleation was necessary. Three such lesions have been subjected to careful pathologic study.

I. Matsukawa (55).—Initial manifestations. Early secondary syphilis. O. S. Iritis papulosa. One dose of arsphenamine. Two months later recurrence of ocular lesion. Pathologic findings. Syphiloma in each the ciliary body and the optic nerve.

II. Verhoeff (56).—Initial manifestations. Early syphilis. Tonsillar chancre. Treatment. One dose of arsphenamine, g. 0. 6. Two months later development of an ocular lesion which failed to improve under antisyphilitics. Blood Wassermann, negative. Pathologic findings. Retinal detachment due to a syphiloma near the papilla involving chiefly the inner retinal layers and only secondarily the disk and choroid. Minor changes in the anterior uvea, probably due to toxins diffusing through the vitreous from the retina. The blood vessels, especially the arteries, of the disk and the affected portion of the retina showed marked proliferative endovasculitis, a main branch of the central artery was almost obliterated by endarteritic processes and more peripherally was thrombosed.

III. Jacoby (57).—Initial manifestations. Early secondary syphilis, roseola. Treatment. Twelve intramuscular injections of mercury salicylate and six intravenous injections of neoarsphenamine totalling g. 3.45. Six or seven weeks after the last dose of neoarsphenamine the following ocular lesion developed. O.D. Descemetitis 'hypopyon. Subsequently hyphæma, exudate within the pupillary region steamy cornea, T. *35 mg* Hg. O.S. Iris hyperæmic, blurring' of the papilla and the surrounding retina, numerous retinal hemorrhages. The right eye was enucleated because of persistent pain in

spite of antisyphilitics and because of suspicion of tumor. Microscopic examination showed a panophthalmia, the characteristic lesion consisting of endo- and perivasculitis with lymphocytic and plasma cell infiltration. Adjacent to the papilla was a syphiloma involving choroid and retina.

In analyzing these ocular lesions the following features are noteworthy.

1. The development of the ocular lesion in patients treated some weeks previously for early syphilis.

2. Severity of the reaction with absence of response to antisyphilitics.

3. Extensiveness of the lesions, even an actual panophthalmia. (Jacoby.)

4. The degree of the exudative reaction. The presence of syphilomas, twice in the anterior uvea, twice peripapillary, and once actually involving the papilla.

5. The absence of fixation in the two patients in whom the Wassermann test was performed. This finding is in accord with the explanation of the genesis of these lesions, namely, suppression of early syphilis with reduction or disappearance of the Wassermann bodies from the blood stream followed by a marked exudative reaction at the site of surviving spirochætes.

Eventually following the appearance of the ocular lesion, as in the case of primary syphilis, there will be a gradual reappearance of complement fixing bodies. In a group of these iridorecurrences previously analyzed (19), the Wassermann was completely positive in two, partially so in three, and absence of fixation occurred in nine. Analogous to the provocative phenomenon occurring as a result of treatment of primary syphilis, among these iridorecurrences with negative Wassermann reactions at the commencement of treatment for the ocular lesion, there was a transient appearance of complement fixation in three.

It is evident that these lesions in no way reflect on the efficacy of the arsphenamines. They are in reality an expression of marked therapeutic potency on the part of the drugs. Such deleterious reactions develop because of failure to sustain suppression of the infection by continuance of treatment. With increased understanding of the action of these drugs and a more rational method of administration the incidence of

neurorecurrences and iridorecurrences has been reduced to almost nil. They occur almost entirely in uncoöperative patients, and with rigid control of early syphilitics they have become uncommon. The baneful results of a single injection of arsphenamine in early syphilis, especially on the ocular structures, can be appreciated by referring to Fehr's statistics. The prophylaxis of these lesions depends upon intensive, prolonged and systematic treatment of early syphilis.

RELATIVE FREQUENCY OF INVOLVEMENT OF THE II, III, IV AND VI CRANIAL NERVES IN NEURORECURRENCES.

Cranial Nerve	*Benario*	*Gennerich*	*Brüning*	*Zimmermann*	*Total*
II.	52	2	2	10	66
III.	18	1	1	4	24
IV.	2	0	0	1	3
V.	7	0	1	3	11
VI.	10	2	2	0	14
VII.	36	6	2	17	61
VIII.	90	8	7	19	124
Total Neurorecurrences.					
	170	25	12	49	256
With Involvement of II, III, IV and VI Cranial Nerves.					
	79	4	4	12	99

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REPORT OF THE ANNUAL CONGRESS OF THE OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM.

By Mr. H. DICKINSON, London.

The Annual Congress of the Society took place in the building of the Royal Society of Medicine, and the clinical meeting at "Moorfields," City Road, on April 19th, 20th and 21st, Mr. C. Howard Usher, of Aberdeen, the President, occupying the chair throughout. The average attendance was nearly a hundred.

Presidential Address.

The President made sympathetic reference to the death, since the Society last met, of Mr. Waren Tay and Mr. Stanford Morton, and extolled their work for ophthalmology. He also reminded members of the broad outlook the Society had maintained during its 47 years, as shown by the inclusion in its membership of physicians, neurologists and surgeons in other departments than the ophthalmological.

He took as his theme

Relationships between Animals' Eyes and Human Ophthalmology.

With the exception of Wardrop's "Diseases of the Eye of the Horse," which was issued in 1819, there was no original work on diseases of eyes in animals by a British author. Yet, especially for teaching purposes, human ophthalmic surgery was associated in various ways with the eyes of animals. The transplantation of cornea, or the substitution of clear cornea from a rabbit's eye for an opaque portion of human cornea was an example from the operative field. He referred to the studies of albinism in man which were conducted by Karl Pearson and Nettleship, with whom the speaker was associated. In this, as opportunities of examining human albinos were very limited, albinotic eyes were exam-

ined in the dog, horse, rabbit, guinea-pig, mouse, bird, etc. Only two birds of those examined were found to have eyes completely devoid of pigment; one a blackbird whose plumage was all white, the other a greenfinch which had patches of canary yellow on its white plumage. A bird with only pure white feathers might have a red pupil and no ocular pigment, or a red pupil and only a small quantity of ocular pigment. It seemed strange that some of the birds' eyes should contain pigment in the pecten when there was no pigment in any other mesoblastic structure of the eye, as the speaker believed that the pecten was wholly derived from mesoblast. But Bernd found an ectodermal origin, and the major portion of the embryonic pecten on the 7th day was of ectodermal origin, the mesoderm forming a relatively inconspicuous part of it. Miss Mann and others had confirmed the two-fold origin of the pecten.

Mr. Usher then went on to refer to the iris color in winter-white animals, and asked whether there was a seasonal variation in the color of the iris of animals which changed the color of their summer coats to white in winter. A number of observations seemed to show that the iris of the mountain hare had less pigment in winter than in summer.

The study of animals' eyes could also help in the study of human eyes in regard to heredity. Human pedigrees were much more difficult to work out than were the pedigrees of animals; also the control of matings and the difficulty of obtaining post mortem examinations were obstacles on the human side. The work now being carried on in this comparative way was likely to be of much value, and to serve a number of useful purposes.

Mr. E. Treacher Collins read a paper entitled

Notes on the Natural History of Retinal Neoplasms.

The conclusions at which he had arrived, on the very elaborate data which he laid before the meeting, can be summarized as follows:

(1) That at Moorfields Ophthalmic Hospital there had been no evidence, during the past 53 years, of any increase in the number of cases of retinal glioma. (2) That retinal glioma was limited to the very early years of life, as it arose

from cells which became highly specialized and soon lost all the capacity they might have had for reproduction. A further point was that this tissue did not contain "mother cells." (3) That cells in metastatic growths of retinal glioma sometimes underwent an increase in size and an alteration in shape, due to a change in their environment, the chief alteration consisting in an increased blood supply, the blood vessels in the primary growth being only terminal vessels. (4) That the uveal tract when invaded by retinal glioma reacted by forming fibrous tissue, contraction of which might cause shrinkage of the growth. When the ciliary body was invaded, the supply of intra-ocular nutrient fluid was cut off, and the loss of this, with the contraction of the newly-formed fibrous tissue, caused the eyeball to shrink. (5) Retinal gliomata were, he said, growths of the neural epiblast, and in their mode of dissemination they resembled carcinomata rather than sarcomata. It was more frequent for them to spread by centrifugal permeation along lymphatic spaces than as emboli in vascular channels. For this reason, secondary growths were more frequent in the vicinity of the eye than in the internal organs. (6) The blood vessels of the retina, its only mesoblastic constituent, might certainly be the seat of origin of capillary angiomata, possibly also of angio-sarcomata. It was necessary, however, to collect more evidence concerning primary retinal malignant growths commencing after middle life before this could be regarded as proved.

LIEUT.-COL. H. SMITH said it had frequently been asserted that malignant disease was not as frequent among vegetarian people in the East as among meat-eating Westerns, but, as one who had had a large experience in both regions he could assert that this was untrue. Many of those who made such statements had only a limited experience in one civil hospital.

MR. COLLINS, in reply, said glioma could not be attributed to diet, as two-thirds of the cases started before birth.

Discussion on the Causes and Treatment of Irido-cyclitis with Raised Tension.

MR. R. AFFLECK GREEVES, in introducing this discussion, said he took it that the discussion was mainly concerned with raised intra-ocular tension in the active stages of irido-cyclitis.

The microscopical examination of eyes excised in a state of glaucoma had shown that in the majority of cases evidence could be found that there was interference with the excretory mechanism of the eye, hence ophthalmologists had become accustomed to think of glaucoma in terms of diminished secretion, rather than as a condition of disturbance in the mechanism of supply of the intra-ocular fluid. Few would deny that blocking of the excretory angle did, in many varieties of the disease, cause the rise of tension. But glaucoma could exist in association with a normal or an increased depth of the anterior chamber, and in the absence of any apposition or adhesion of the iris root to the corneal periphery.

He held the view that in iridocyclitis the deepening of the anterior chamber depended on osmosis. All inflammatory exudates greatly exceeded normal fluids in colloid constituents and hence also in osmotic power, and while a highly albuminous exudate was being continually poured out into the anterior part of the globe, a redistribution of water would take place, the colloids in the anterior chamber would take up water, and the vitreous body would lose it, and consequently the lens and iris would move back. Recent researches showed that the fluid was a transudate from the capillaries of the ciliary body. Duke Elder showed that equilibrium between the intra-ocular fluid and the blood could be maintained normally by the greater osmotic power of the colloids in the blood tending to attract fluid, *versus* the greater actual capillary pressure tending to drive fluid out, and that the chemical composition of the blood and intra-ocular fluid respectively agreed with the theory of a transudate. Intra-ocular pressure, was influenced Mr. Greeves said, by altering the equilibrium level, by changing the relative compositions of the blood and aqueous, a condition which must occur in inflammations of the ciliary body, owing to increased permeability of the capillary walls. Probably these considerations were factors in the causation of glaucoma in cases of serious iridocyclitis. If the mechanism were rendered less adequate by partial blocking of the spaces of Fontana with cells or by senile changes, such as thickening of the fibers of the ligamentum pectinatum, it might not be able to function sufficiently.

Glaucoma with iridocyclitis occurred most frequently in the

middle-aged and elderly, in many of whom the anterior chamber was shallow, and the anatomical conformation of the eye was that associated with a predisposition to glaucoma. It was of a different class from that of iridocyclitis with raised tension in which the anterior chamber was normal or increased in depth, in that the eye was already predisposed to glaucoma, and an inflammatory process sufficed to induce the condition. It was made worse by the use of mydriatics, but meiotics often reduced the tension. Still, mydriatics were not always successful in those with deep or normal anterior chamber. In a few cases he had noticed that at first atropin raised the tension while eserin lowered it, but after treatment with a meiotic for some days, with a successful lowering of tension, atropin could be used with impunity. Writers on ophthalmic topics showed a considerable difference of opinion on the question of mydriatic *versus* meiotic treatment in these cases, and a number of expressions of view were quoted by the reader. His own general line of treatment was to use a meiotic where the anterior chamber was shallow and the appearance of the eye suggested a predisposition to glaucoma. In cases with a deep or normal anterior chamber he instilled homatropin, as it was better controlled than atropin. If this was beneficial he continued with atropin treatment. But if tension remained raised, or was increased, he recommenced meiotics. If a definite improvement followed the latter and tension remained normal for some days, he again used a mydriatic.

Mr. W. H. McMullen said that so great was the variety of manifestations of the disease that no rigid classification of cases was practicable. Three types, however, covered the majority. These were: (1) acute iridocyclitis with increased tension soon after the onset of inflammation; (2) cases resembling acute or sub-acute primary glaucoma in which careful examination showed uveal inflammation; (3) cases of chronic iridocyclitis in which increase of tension occurred months, even years, after the commencement of obvious inflammation.

He referred to the two schools of teaching concerning the treatment of acute iridocyclitis. One laid stress on the danger of provoking high tension by mydriatics, advising caution with the latter, and should slight rise of tension occur,

the mydriatic should be stopped and a meiotic substituted. The other school emphasized the great value of mydriatics, which should, in their view, be used boldly, though the surgeon should be prepared to operate if there occurred any considerable rise of tension. Mr. McMullen's leaning was towards the second school. With regard to indications for operation, if there was considerable pain, steaminess of cornea, and finger estimate of tension was plus one or more, operation, in his view, should not be delayed more than twenty-four hours. Choice of operation he discussed in some detail.

In concluding his paper Mr. McMullen said the chief thing to consider was whether it was probable that the rise of tension was due to temporary conditions caused by the iridocyclitis, or whether there were permanent changes in the eye, rendering it liable to persistent or recurrent increases of pressure. In the first case one should energetically treat the iridocyclitis while trying by other means to reduce the intra-ocular pressure; while in the second case one should operate without loss of time by a method whose object was to secure permanent relief of tension.

Sir Arnold Lawson said he had not had a case in which the use of a meiotic gave satisfaction. He felt that the use of atropin for cases of the kind under discussion could not be wrong, and when it did not act as it might seem it ought to he thought it was usually because the cause of the inflammation was not under control. Often the causal factor was obvious: a positive Wassermann or oral sepsis, though in these days he thought there was a tendency to ascribe to oral sepsis any trouble which happened to exist in the body, and that was a real danger; the toxic seat might equally be in any other part of the body. Paracentesis, though glibly spoken of, was, in his experience, disappointing, especially as it might need to be repeated. He favored anterior sclerectomy with a small iridectomy. Iridocyclitis must be regarded as of secondary importance as compared to the glaucoma.

Mr. J. Gray Clegg said that of 146 cases of iridocyclitis, 50 (38 per cent) presented definite raised tension which was not due to exclusio pupillæ. The cause was syphilis in 6, tubercle in 2, sepsis in 12, in 35 no cause was found. Treatment was medical and surgical. Only when medical means

did not restore normal tension to the globe did he operate. If a mydriatic had been employed, he discontinued it for a few days. Often he was able to reduce tension by the use of dionin, the method of which he detailed. He did not persevere with medical measures for longer than a week. Non-operative means succeeded in 23 of the 55 cases, though abnormal tension was liable to recur. Paracentesis, when that was called for, might have to be repeated on two or three occasions. The ideal was to produce a permanent drainage from the anterior chamber, and he had for some time employed the *2mm* sclerocorneal trephine method, taking care to remove the whole of the disk. He was now trying the Glaucosan solutions suggested by Hamburger of Berlin. If the claims made for it were substantiated, it would do much to solve the problem.

Mr. T. Harrison Butler said that in the acute, florid cases—the so-called medical cases—the use of eserine was apt to be disastrous. Atropine should be employed, and pushed. As most of the cases occurred in females, it was reasonable to have their genitalia examined; that was his custom, and a septic focus was found there in quite a number of cases.

Mr. A. L. Whitehead agreed with Mr. Butler's remarks as to the frequent site of sepsis in female cases. In a large number of his cases there had been some definite—usually septic—condition of uterus or vagina, though in many cases in both sexes no cause could be found. As to treatment, it was essential to try first to find the cause and treat that. For local treatment he attached great importance to heat, both dry and moist, which could be conveniently applied by electricity. Leeches to the temple were also valuable. Paracentesis should not be repeated more than twice. Operative procedure in these cases was sometimes disastrous. He had also seen bad effects follow the use of meiotics.

Col. H. Herbert, Mr. Christie Reid and Col. Lister also spoke and Mr. Greeves and Mr. McMullen replied.

Another discussion which was held was one on

The Diagnosis and Treatment of Inflammatory Affections of the Orbit.

Mr. A. F. MacCallan opened with an elaborate paper from the ophthalmic standpoint. He suggested that the

following was a convenient classification of the causes of such inflammation:

(1) Injuries.
(2) Primary osteomyelitis.
(3) Acute dacryoadenitis.
(4) Spread of inflammation from neighboring parts, as in (a) Panophthalmitis; (b) cavernous sinus thrombosis; (c) infected wounds or abscesses of face or eyelids, also erysipelas; (d) acute pharyngitis (including scarlet fever); (e) acute periodontitis and maxillary periostitis; (f) infections of the accessory sinuses; (g) tubercular meningitis.
(5) Septicæmic conditions.
(6) Syphilis and Tubercle.
(7) Orbital myiasis, aspergillosis, actinomycosis.

These the reader passed separately in review, and reported a number of apposite cases.

Dealing with treatment, Mr. MacCallan said this resolved itself into the evacuation of pus in the orbit—if present—and a careful search for the prime cause of the inflammation, in which one looked for the coöperation of specialist colleagues, not forgetting teeth, bladder, prostate, etc.

Mr. Norman Patterson entered at length into the rhinological aspect of the matter. He said that in the majority of cases the inflammatory conditions affecting the orbit were secondary to an infection of the nasal sinuses, and children were especially liable to them. His own view was that only rarely were the antrum and the sphenoidal sinuses responsible for the orbital condition. In every case a thorough examination of nose and accessory cavities should be carried out. A chronic suppuration in nasal sinuses might be complicated by orbital inflammation and abscess. Congestion and tumefaction should specially be looked for in the middle turbinate region. When pus was seen, an attempt should be made to trace it to its site of origin. When gross destruction of the party-wall between the infected sinus and the orbit had occurred, pressure on the orbital swelling might cause an increased flow into the nose. Sometimes it was difficult for

even an expert to quite exonerate all the nasal sinuses. Orbital inflammation might occur very suddenly soon after the onset of a nasal catarrh, pain being later increased on ocular movement. In inflammation of the frontal sinus there were frequently swelling and tenderness of the tissues covering the anterior wall. The orbital swelling might be exquisitely tender, especially in the region of the inner canthus; it was elastic, might pit on pressure, and occasionally fluctuation was elicited. The abscess might rupture externally, leaving a fistula. Transillumination should be carried out in all cases of orbital inflammation. The antrum on the affected side might be dark, and exploratory puncture might be important in treatment as well as in diagnosis. The treatment Mr. Patterson considered under the three heads: general, treatment of the nasal condition, treatment of the orbital complication. In each class he went into the measures with great thoroughness.

Dr. P. Watson-Williams said the three main points for consideration were: (1) whether an orbital or ocular affection was caused by disease in the nose or accessory sinuses, and (2) which sinus or sinuses caused the orbito-ocular complication; (3) what was the pathological nature of the nasal disease? He considered that an inflammatory swelling in the orbit, with tenderness and resistance on pressure, suggested a nasal origin if associated with displacement of the bulbus or its forward dislocation. When eye movements were attended with pain and were restricted this was almost a certainty if a fistula led to a nasal sinus. He went into the subject in detail.

Mr. Somerville Hastings also considered the matter from the same standpoint, his special purpose being to stress the frequency with which swelling and infection of the orbit took place in consequence of syphilis. Another condition he sometimes saw as a sequel of syphilis was a redness and swelling of the inner canthus and vicinity.

Mr. E. D. Davis spoke of 33 cases of his own in which there was œdema or swelling of the orbital contents and which were sent to him by ophthalmic surgeons for an examination of the nose to be made. In 16 of them there was frontal sinus suppuration, in 7 ethmoidal sinus suppuration, in 5 orbital

tumor, in 2 optic nerve tumor, and foreign body, suppurating cyst and metastatic panophthalmitis in one each. Thus 23 of the cases arose from nasal sinus suppuration. The treatment of inflammation of the orbit or of an orbital abscess arising from the nose was always urgent, more urgent, indeed, than an acute mastoid condition. He described his usual operative procedures. Romer stated that twenty per cent of the cases of orbital cellulitis were followed by optic atrophy, a complication which was to be expected in a severe or long-lasting case.

Mr. Harrison Butler stressed the importance of acute cases, which might die, apart from the calamity of losing their sight. In one case the pus was situated only in Tenon's capsule, and an incision there to liberate the pus resulted in an immediate clearing up of the case.

Col. Lister referred to a case of inflammatory swelling of the orbit due to a suppurating hydatid cyst, which occurred in India, and he said this cause should be included in any category of possible causes.

Dr. G. Mackay spoke of a commoner form of cyst which might cause orbital inflammation, namely a dermoid cyst, and related a case of the kind.

Mr. A. L. Whitehead referred to the help given in these cases by a good skiagram. He also alluded to a group of cases of orbital cellulitis in children, without much proptosis but with considerable fixation of the globe. A few days' rest and fomentations usually cleared the condition up.

Mr. Jameson Evans said that there were some cases of cellulitis which followed forceps delivery. He had encountered chemosis of the lower part of the conjunctiva in which there was no infection. It seemed to have followed thrombosis in some of the orbital veins. Nothing could be done for these cases, which eventually, after a long time, settled down.

Mr. A. F. MacCallan, C.B.E., M.D., Cambridge, F.R.C.S., presented "A Report on a Series of 100 Consecutive Refraction Cases with full vision after correction. Indications for Reference to Other Branches of the Medical Profession of those showing Evidence in the Eye of Toxic Conditions."

The clinical observations were made on a series of 100

patients seen in private consultation. The series was commenced in August 1927 and included all private patients examined who could be improved by glasses to the usual standard of normal vision. During the period under survey 39 other patients were examined whose vision could not be improved to the normal on account of obvious pathological changes in the eyes. The ocular changes which have been shown to be associated with condition of focal sepsis are numerous, but those noted by Mr. MacCallan in this particular series of cases were blepharitis, episcleritis, opacities of the lenses as seen by ordinary focal illumination, opacities in the vitreous seen with the Slit-lamp, and changes in the retina in the region of the macula.

After investigation the conditions of sepsis in the body calling for surgical intervention were found to be appendicitis 1 case, enlarged septic tonsils 2 cases, suppurating antrum 1 case. The cases of dental sepsis were more numerous, 42 patients being referred to their own dentists for treatment at the discretion of the dentist. Of these cases radiographs of the whole mouth were made in 33 patients with the result that the appearances which are characteristic of apical abscesses were seen in 22 of them. Most of these abscesses were shown to have been actually present by extraction of the diseased tooth, though many other teeth were condemned by the dentist which on extraction were found to have the apices infected. There was also one case of a dental cyst with apical abscesses in which the bone of the mandible was dangerously thin.

The patients were almost entirely drawn from the upper middle class which makes the dental findings much more striking than if they were drawn from a hospital clinic. To find 22 cases of apical abscesses among 100 private patients who came to an ophthalmic surgeon for glasses seems to indicate the need for an increased use of radiography by dentists and increased suspicion of every dead tooth.

A number of radiographs by Dr. Coldwell, Radiologist to Westminster Hospital, were thrown on the screen and demonstrated by Dr. A. Livingstone, Director of Dental Studies at King's College Hospital. Sir William Willcox expressed his opinion of the importance of determining the presence or

absence of focal sepsis in all medical cases and of the interest he felt in Mr. MacCallan's communication.

A detailed description of each of the 100 cases is appended to the paper which will be published in the *Transactions* of the Ophthalmological Society which appears in the autumn.

A clinical meeting and discussion followed at "Moorfields," a dinner, papers as follows: Mr. M. S. Mayou, Coats' Disease, the juvenile form; Mr. G. Alexander, The Immediate Removal of Congenital Cataract; Mr. F. Williamson-Noble, Retinoscopy and the Pointolite Lamp; Dr. Houwer, On the Origin of Melanomata of the Uvea; Mr. Chas. Goulden, (1) Some Unusual Types of Acquired Cataract, (2) The Illumination of the Field of Operation in Ophthalmic Surgery.

The Bowman Lecture was delivered by Professor Elliot Smith, who took as his subject "The New Vision."

The concluding event was a visit to the Lister Institute of Preventive Medicine.

REPORT OF THE SECTION OF OPHTHALMOLOGY, NEW YORK ACADEMY OF MEDICINE.

By Dr. THOMAS H. JOHNSON, Secretary.

MEETING, MARCH 19, 1928. DR. BERNARD SAMUELS, CHAIRMAN.

Dr. Francis W. Shine: A **case of bilateral sarcoma of the uveal tract.**

The patient, a male, age 35, first seen March 7, 1921. He had always been aware of the presence of a small "birthmark" at the lower part of the pupil of right eye. In 1916, while at target practice was struck in right eye by the firing pin of a rifle resulting in a "hemorrhage" which absorbed in about one month. On March 6, 1921, suddenly developed severe pain in right eye and it was noticed that the pupil was quite red. Examination next day showed lower outer quadrant of iris to be seat of a brownish black, deeply pigmented mass protruding forward into anterior chamber together with considerable remaining hemorrhage. Cornea, lens, vitreous and fundus normal. Vision $\frac{1}{60}$; transillumination showed dark circular shadow. Left eye normal; Vision $\frac{1}{60}$ plus. Enucleation of right eye advised. This was done at a Government Institution after several treatments of radium had been given. I am told that the diagnosis was confirmed by microscopic section, but about this time the Government gave up the use of the Polyclinic Hospital and the specimens were lost.

Patient was not seen by me again until Sept. 9, 1924. He then stated that for two weeks he had noticed vision failing in the left eye. Examination showed a large choroidal tumor in the upper portion of the fundus; dense shadow on transillumination; Vision $\frac{1}{60}$. Diagnosis made of sarcoma of choroid and this was concurred in by a number of surgeons

who saw the patient. Physical examination and other tests all negative. Was seen from time to time with gradually failing vision until April 24, 1927, when the eye was blind, hard and extremely painful. Eye was enucleated and pathological examination of the specimen showed a melano-sarcoma. Patient remains up to present time in good health.

DR. SIGMUND A. AGATSTON read a paper on cases of **squint** operated by a new method of **recession without tenotomy.** "I can safely state that 'recession' is looked upon with favor by surgeons who have given this operation a fair trial. The technique which we have been using, though simple, is subject to errors, which are sometimes responsible for imperfect results. Thus, if the caruncle has not been carefully dissected, it may show a sinking. If the muscle ligature is not carefully tied, the muscle may slip back, with the result of too much recession. It has occurred to me that our method can be still further simplified. I think most of you are familiar with the operation.

"In a general way, it consists of exposure of the internal rectus; dissection of the conjunctiva and caruncle; insertion of suture; complete tenotomy; and retro-placement of the insertion to the sclera at a point posterior to the original insertion. I think I have succeeded in eliminating a few steps of this operation. The abbreviation is based on the theory that the good effect of the operation is due to the position of the insertion nearer to the equator of the globe. So that it makes no difference whether a tenotomy is done, so long as the tendon becomes adherent to the sclera at a point to which it was our intention to move the insertion. A horizontal incision is made above the muscle. This incision takes in the conjunctiva and Tenon's capsule. Thus the sclera is exposed. Holding the muscle to one side, two double-armed sutures are passed through the sclera at two points on the line at which we decide to place the insertion. Of the lower suture, the two needles are passed through the lower half of the muscle and conjunctiva. Of the upper suture, one needle is passed through the upper part of the muscle, and the other needle through the conjunctiva and Tenon's above the incision. No tenotomy is performed. The sutures are tied. One word about the scleral suture. There is no danger of piercing the sclera

if the needle is properly inserted. Place the needle perpendicular to the sclera until the needle catches the superficial fibers. Then pick up these fibers by slowly turning the needle holder. This act of rotating the needle holder will prevent the point from going deeper into the sclera. If the scleral bite is insufficient the needle simply slips off. The muscle becomes adherent to the sclera and the result is the same as in the ordinary recession. The conjunctiva and caruncle have not been disturbed. The operation is simpler and the cosmetic result better, as there is absolutely no chance of sinking of the caruncle, or disturbance of the semilunar fold."

Dr. Louise H. Meeker gave a screen demonstration of some interesting **pathological pictures in the eye.**

Two general types of eye lesions were shown.

First:—A series of slides illustrating various wounds of the eye, accidental and operative, and the associated condition necessitating enucleation. The lesions ranged in time intervals from 4 hours to 1 day, from 1 to several days to 1 month, from 6 weeks to 8 and 12 months, from 1 year to 2, 4, 17 and 47 years. The immediate associated pathology varied from loss of lens and vitreous to prolapse of iris and ciliary body, iridodialysis, detachment of retina and extensive intraocular hermorrhages and hemorrhages in the optic nerve sheaths. The later pathology included adherent leukoma, iridocyclitis plastica, traumatic cataract, secondary glaucoma and phthisis bulbi. Symphathetic ophthalmia followed in one case only in the eye sustaining the initial wound 47 years previously. Rotation of the lens on its transverse axis followed a wound of the cornea in a young subject. In two cases there were vitreous abscesses, one in the anterior vitreous and the other (rarer) the posterior vitreous. Other disastrous sequelæ were the implantation of corneal epithelium in the anterior chamber in one instance and in the lens capsule in the other instance.

Second:—A series of slides illustrating several rarer and quite diverse eye lesions. Included in this group were retinitis interna and externa. Painful phthisis bulbi due to a new growth in one case and to repeated hemorrhages with foreign body reaction in another case. Scleritis, anterior circumscribed, diffuse deep scleritis and scleral ectasias, an-

anterior, equatorial and posterior. Hypermature cataract and bilateral congenital total cataracts. Lastly obliterating endarteritis in the long posterior ciliary artery of a diabetic eye together with earlier stages in other episcleral vessels found in diabetes.

DR. MELVIN G. HERZFELD gave a screen demonstration of the **pathology of the crystalline lens.**

MEETING OF APRIL 16, 1928. DR. BERNARD SAMUELS, CHAIRMAN.

DR. WENDELL L. HUGHES presented three cases:

CASE 1. **Anomaly of distribution of the vessels on the disk** (isolated arteries). (To be published in full.)

The introduction of cilia into the anterior chamber of the eye usually follows an operative incision, or accompanies a penetrating injury of the cornea. A severe inflammation in the form of an iridocyclitis is set up, and when this subsides complications may ensue such as, "foreign body cysts, margaritomas, or epidermoidal tumors of the iris, with glaucoma, blindness or loss of the eye."

Rothmund collected 36 cases of pearl cyst of the iris, in three of which cilia were seen in the cyst wall. Paderstein reports a case of 2 cilia in the anterior chamber with attempted removal and cataract formation. In Barr's case the eye was quiet for 12 years, and then an iridocyclitis was set up, following a minor blow on the head. Rubrecht reports another case of cilia in the anterior chamber, as also have R. A. Hughes (quoted by McKee) and Fox, recently.

CASE REPORT: This man aged 74 presented himself at the clinic of Dr. Weeks at Bellevue Hospital for impaired vision. During the course of the examination two cilia were found adherent to the anterior surface of the iris of the left eye. On further questioning the following history was elicited:

Eight years previously while starting a nail with a hammer he gave it a glancing blow, causing it to flip up, and the end of it entered the left eye. The eye was red, photophobic and painful for about 6 mos. afterwards, and he states that the vision has not been normal since. No history of other trauma was obtained.

The left cornea now presents an irregular scar extending thru all the layers of the cornea, which is roughly horizontal,

about two millimeters in length situated at the junction of the upper and middle thirds of the cornea, directly subjacent to the margin of the upper lid in ordinary forward gaze. In the iris there is atrophy of the pigment ring at the pupillary border, and a few clumps of pigment on the anterior lens capsule. Directly behind the corneal scar, the iris is adherent to the lens, where there is a small opacity in the lens cortex. The nail having apparently impinged the two lashes, passed thru the cornea, and barely entered the lens, carrying the margin of the iris along with it. The iris reacts normally except superiorly at the site of the synechium. In the upper nasal quadrant of the iris, is a segment that is discolored brownish.

There are two cilia enmeshed in the superficial layer of the iris in its upper temporal quadrant. These pass downwards, their tips being free in the nasal portion of the anterior chamber. There are fine dark brown pigment granules of microscopic size on the anterior surface and sides of the lashes along their thicker portions where they are adherent to the underlying iris.

One of the lashes was broken off near its root presenting a jagged edge, the other was uprooted, its bulbous expansion being complete. The conclusion is, of course, that the lashes were carried in by the nail at the time of the accident 8 years ago, and became attached to the anterior surface of the iris by the exudative changes attending the iridocyclitis that was set up.

The question of treatment depends on the history. All recently acquired cilia in the anterior chamber of the eye should be removed. If the cilia have been present for a long time, they may safely remain undisturbed as long as no complications ensue. Should any serious secondary conditions arise due to the presence of the cilia they should be removed. Any eye which contains a lash with its root-bulb intact should be regularly inspected for growth of epithelial cells, and cyst formation.)

CASE 3. **Angioid streaks of the retina.** (To be published in full.

DR. WEBB W. WEEKS: **Lantern slide demonstration of Lagrange operation.**

The Lagrange operation is an anterior sclerectomy with a complete or peripheral iridectomy. The object of the operation is to establish drainage for the intra-ocular fluids by way of the supra-choroidal and subjunctival spaces. This operation is indicated in very early or late stages of chronic simple glaucoma. Briefly reviewing the pathology of the parts concerned with the lantern slides, the operation was depicted in five steps. Complications likely in each step were spoken of and measures of avoidance indicated. Speaking of the post-operative progress, the appearance of the resultant fistulous cicatrix was shown two weeks and one year after operation. The modification of this operation by Morax of Paris was shown in lantern slides and advocated for more general use in cases of chronic simple glaucoma.

DISCUSSION: DR. BERENS said that he had been using a modification of the Lagrange operation for several years.

A flap is dissected down which is made exceptionally thick just above the limbus; a keratome incision is made *2mm* above the limbus; which is *4mm* broad. A complete iridectomy is performed, attempting to obtain as much of the root of the iris as possible. The overhanging edge of the sclera is bitten away with a narrow punch, particular effort being made to excise the sclera in the extreme angles of the wound. The wound is closed by a running paraffined silk suture beginning and ending in the conjunctiva of the canthi which is not tied, and the wound edges are crushed together by means of mouse tooth forceps. Three per-cent atropine is used for several days, and this is followed by a ¼% solution of hyoscin until all signs of inflammation have subsided. Massage is begun as soon as the anterior chamber tends to be restored. Owing to the particular care exercised in closing the wound a large area of the conjunctiva may be distended by the fluid. Excising the sclera well into the angle of the wound in the attempt to make a long filtering cicatrix usually prevents the thin filtering bleb which frequently is seen after the trephine operation. As two of his patients had thin filtering cicatrices in spite of this technic, he has recently experimented in dogs with Doctor Wilmer's Tenon's capsule graft, using the trephine and the technic just described. Because the trephine operation with Tenon's capsule transplant had been performed

in only two cases and the technic just described with the Tenon's capsule graft in two cases, it was too early to draw conclusions. The cases he saw which had been operated on by Doctor Wilmer using the Tenon's capsule graft, made him feel that the operation was worthy of trial since it not only thickened the covering of the wound but also apparently tended to make the area of filtration broader.

DR. CHARLES W. STEVENS: **A stage for the demonstration of optical phenomena.**

Anyone who undertakes the task of teaching physiological optics to a group of medical students is at the outset confronted with the fact that the great majority of his pupils are surprisingly lacking in information in regard to the elementary principles of mathematics and physics. Much time must therefore be spent in preliminary demonstrations of the fundamental laws of optics before approaching the subject of the eye as an optical instrument. Any method, then, which enables us to present these first principles in an easily comprehensible manner is very welcome. Dr. Alfred Cowan of the University of Pennsylvania has recently issued a little book, *An Introductory Course in Ophthalmic Optics*, in which he gives a number of excellent devices for enabling the student to work out for himself the laws of reflection and refraction, and among other things he suggests an optical stage in which various forms of apparatus can be quickly and readily adjusted for the demonstration of optical principles. The optical bench with azo lamp and saddle stands is standard equipment supplied by the Carl Zeiss Company. Lens and screen carries can be supplied by any friendly optician, thus allowing the use of ordinary trial case lenses. Other accessories such as adjustable mirrors, smoke box, fluorescein tanks, etc., are products of the home work bench and the tea cart is a discard from the medical school library. Such an apparatus has the advantage of facilitating accurate work, is easily and quickly set up, and enables one to exhibit very beautiful and convincing demonstrations. Many interesting experiments are also described in a book entitled *Light* by Lewis Wright. I present this apparatus to you not as being in any way original, but as a method which has proved itself to be a distinct and efficient aid in instruction in optics.

Dr. Aryeh Feigenbaum (Jerusalem). **The influence of illumination on intra-ocular pressure in normal and glaucomatous eyes.**

In glaucoma an increase of intra-ocular pressure after a stay in the darkness and a decrease after illumination is often to be found. This "dark-light test" can be shown in the majority of normal eyes too, although faintly. This reaction is especially characteristic of simple and chronic-inflammatory glaucoma with a shallow anterior chamber (with some exceptions in cases of secondary glaucoma). Differences in the amplitude of fluctuations can be of differential-diagnostic value with regard to the forms of glaucoma and of a diagnostic value in early glaucoma.

According to Gronholm and Seidel these changes in pressure are due to the width of the pupil, varying with different degrees of illumination. This explanation must, however, be rejected for several reasons. The "dark-light test" is not less typical in pilocarpinized and homatropinized normal eyes as well as in iridectomized and pilocarpinized glaucomatus eyes. Furthermore, an experimental illumination carried out on a series of blind eyes in glaucoma patients caused a parallel decrease of intra-ocular pressure in the other eye too, which was tightly protected from light.

We must recognize in the periodical changes of pressure during day and night as well as in the fluctuations occurring in experimental dark-light tests, rhythmical processes, analogous to other functions of the living organism that belong to the vegetable nervous system. A pathological increase of the fluctuations in glaucoma is thus to be sought in a functional inferiority of the vessels. The changes are most probably the results of a direct light effect on the vasomotors of the capillaries of the iris and ciliary body. In unilateral illumination the stimulus is carried over to the other side by a vasomotor reflex. A kind of light hygiene should be applied to glaucomatous eyes.

Dr. Aryeh Feigenbaum (Jerusalem). **Temporary and permanent disturbance of the dark adaptation in glaucoma.**

In glaucoma the light sense is frequently found to be impaired. The impairment is the direct result of ocular hypertension. A temporary hypertension provokes a dete-

rioration of dark-adaptation which can be greatly improved by decrease of pressure. Hypertension when established over a longer period or recurring frequently, will provoke permanent injury of the nervous elements concerned, and will cause permanent disturbances of dark-light adaptation.

Pilocarpine has no effect on the course of dark-adaptation other than that the latter is lowered by miosis.

DISCUSSION: DR. KNAPP: I am sorry that Doctor Feigenbaum's time was so restricted, as the report of his interesting investigations was much too brief. I should like to ask Doctor Feigenbaum whether it is not curious, in view of the findings that ocular tension rises in darkness, that a mild attack of increased tension is often relieved by sleep; furthermore, if the ocular tension always rises during the night, would it be desirable to wake patients with glaucoma for the purpose of administering drops?

DR. P. A. CHANDLER: We have not done work on the influence of illumination on intra-ocular pressure in normal and glaucomatous eyes. I am very much interested to learn of the rise in tension in these patients after a stay in the dark, and of the rise of the light threshold when the test of the light sense is continued for a longer time than usual. We have not observed this phenomenon, probably because we use pilocarpine until no pupillary reaction remains, before testing the light sense. The pupils are fixed because the pupillary size influences the amount of light reaching the retina. The difference in the light sense between the normal and the preglaucomatous eye is often but slight, and we feel that the pupillary factor must be controlled in order to make our results significant. When we find a patient has an increased intra-ocular tension or the smallest field change indicative of glaucoma we no longer test the light sense, but rely on the ordinary clinical tests in following the case. It seems to me that Dr. Feigenbaum's tests would be most useful in those borderline cases where the light sense does not give us definite enough information. Here the additional data might be enough in many cases to give us a diagnosis.

CONCLUSION: DR. FEIGENBAUM: Knowing the important part which the width of the pupil plays in adaptation, I fixed the pupils in about one half of my examinations by pilocarpine.

The other half I left uninfluenced by any medication because only in this way was it possible to detect the influence of hypertension caused by the darkness. For the same reason no fixation of the pupil by homatropine could be employed; we would not know whether the hypertension was due to a stay in the darkness alone, or to the medication.

At any rate, it is advisable to administer the last doses of pilocarpine late in the evening, shortly before going to bed. Often this is sufficient to keep the tension down until the morning. May I mention the interesting fact that already ophthalmolgists of the older generation (If I am not mistaken, Schmidt-Rimpler) advised keeping a light in the bedroom of the glaucomatous patient during the night.

DR. SELIG HECHT: **Visual Acuity.** (To be published in full.)

ABSTRACTS.

Contributions to the Comparative Anatomy of the Reptilian and the Amphibian Eye, chiefly based on ophthalmological examination. By GEORGE LINDSAY JOHNSON, M.A., M.D. (*Phil. Trans. Royal Soc. of London*, Series B, Vol. 215, pp. 315–353. Plates 20–25.)

Dr. Johnson has, in this original work, distinctly won new laurels in a field that is peculiarly his own. In 1901 he contributed to the Royal Society (also through his friend Prof. Hans Gadow to whom he has acknowledged his indebtedness for assistance and encouragement) a larger work on the mammalian eye. The present paper may, therefore, be regarded as a supplement to the major treatise.

In the restricted space permitted the reviewer we propose to say a few words in an attempt to emphasize rather than to criticize the author's statements and conclusions. In another place we hope to be able to publish some further observations on the eyes of reptilian and amphibious vertebrates that may, perhaps, extend our limited knowledge of this subject.

The present paper opens with a brief review of the work already done on the eyes and vision of vertebrates. In it the author states the difficulties attendant upon an examination of the fundus of Fishes—the physical obstacles predominating; and it certainly is almost impossible to hold in a fixed position a live, wriggling, slippery animal for the purpose of examining the ocular interior and background through a round lens of a highly hyperopic globe. Moreover, postmortem examination of fish is much less satisfactory than of Birds in whom, as the reviewer has shown, the five minutes before death and the five minutes after breathing has ceased seem to furnish a satisfactory period for ophthalmoscopy; the pupil, unaffected

by mydriatics, then dilates and quiet, satisfactory background pictures can be secured. The piscine eye, on the other hand, undergoes such rapid changes after death that neither the mirror nor the microscope furnished much information of value.

As for the eyes and eyesight of Birds, Lindsay Johnson believes that the subject has been sufficiently treated by Casey Wood of Chicago. Therefore, Amphibia and Reptiles remain; and these subclasses constitute the principal topic of his thesis.

One of the chief attractions of the essay is the fact that the writer does not minimize the laborious character of his enterprise and although it is unfortunate that these obstacles may discourage other students of comparative ophthalmology it is only right that they be plainly stated. Only those of us who have attempted during field work to examine the eyes of all sorts of animals by mountain, jungle and stream, generally under a well covered umbrella or in a smothering tent,—only those can realize the difficulties of pursuing this form of scientific research. Still, with care and patience, the eyes of most reptilian and amphibian forms can be made to yield physiological information of some interest and importance. This is especially true if the observer can command efficient assistance, and a well-aired, dark room attached to a zoo whose denizens he may examine at leisure. If not an artist himself he shou d train one to help him record his findings. This scheme of an ophthalmic artist as an aid to the student of comparative ophthalmology in original examinations of the eye *intra vitam* will make an instant appeal to every ophthalmologist. Without him the work is robbed of much of its value as a research.

The principal obstruction is a small pupil. Many amphibia and reptiles have pupillary openings that, *ad maximum*, measure less than *2mm* in diameter, and in these cases it is only by piecing together fleeting and partial views of the fundal picture that one can form any worth-while idea of the background as a whole. Johnson has employed only the direct method in his ophthalmoscopic examinations, but he does not tell us what instrument he employed in his work, so that it may be well to add that the latest type of self-luminous

scope with a small ocular aperture has given results that, by the reviewer at least, have not been otherwise obtainable.

Our experience with artificial mydriasis in reptilian eyes seems to have been less encouraging than that of the writer. Dr. Johnson remarks that "in quite a number of cases the pupils are unaffected by mydriatics." One wishes that he had informed us in what species he, with his wider experience, found them useful, as we cannot recall a single instance in which euphthalmin, atropia, or any other mydriatic, or cycloplegic dilated the reptilian eye except on those occasions when it acted as a poison, and one suspects that the resulting mydriasis was a lethal effect.

The danger of poisonous snakebite in making ophthalmic examinations is no figment of the imagination. Plate 24 of the present work shows a fundus drawing of *Naja tripudians*. Our experience of the Indian Cobra both captive (in a glassed cage) and wild (in Ceylon and at a safe distance) has led us to admire the reckless courage of the artist who painted *that* picture, the assistant who held the snake by the back of the neck and, above all, the ophthalmologist who "scoped" his background. Science owes them all a debt that cannot be paid.

Minor dangers that confront the observer are obvious down the whole line of research. "We (my artist and self) never succeeded in making a good sketch of a rattlesnake's fundus," remarks Johnson. Neither has the reviewer; mainly because he has never tried the experiment. Furthermore he expects to confine his attentions to the non-posionous Colubridæ and similar genera!

Tortoises and turtles are also nearly impossible subjects for ophthalmoscopy. Those of us who have in childhood played with Box Turtles and other chelonians can appreciate the difficulties one might have with an animal who, at the approach of man, conceals his head in a bony carapace.

The eyes of Alligators and Crocodiles—American examples of which are represented in Dr. Johnson's list—are comparatively easy subjects. They may be lassoed and held in place with little difficulty.

The external eye and *fundus oculi* of most Lacertilia (perhaps our Gila Monster, *Heloderma suspectum*, forms one of the exceptions) may be examined without danger or inconvenience.

We know of few chapters on the *lids* or reptiles and amphibia that furnish more satisfactory reading than that given us by the author. Especially well described are the *membrana nictitans* of reptilia and its homologues in other vertebrates. This "third eyelid" has a decidedly practical interest for the ophthalmologist; and he should not forget that the same remark applies to the lachrymal apparatus. How much more intelligently may one approach a study of the anatomy and morphology of human eyelids and tear passages if one has first gained a working knowledge of the histology of these organs in the other vertebrates. Those who have not ready access to the *Philosophical Transactions* will find these subjects fully detailed and illustrated in the reviewer's *Enclyclopedia of Ophthalmology*. There is no chapter in comparative anatomy of more sustained value than a rational account of the varied methods by which the external eye of the different vertebrate species is protected, cleansed and kept in order for taking part in the function of vision.

The *pupils* of amphibia, as everyone who has examined a frog's eyes has noticed, are quite wide; consequently these animals furnish admirable subjects for ophthalmoscopic examination. That student or practitioner who has never seen a frog's fundus has missed something in his collegiate career. It was because of the large pupils and the docility of these amphibia that the reviewer and his artist (Miss Mabel Satterlee) were able some years ago at the Tropical Station of the N. Y. Zoological Society in British Guiana to secure satisfactory drawings of the eyegrounds of several South American species—notably of *Bufo marinus*, *Leptodactylus pentadactylus*, and *L. mystacinus*.

Johnson properly remarks that the pupils of these tailless amphibians have, generally, constantly round pupils, but there are all sorts of exceptions to this rule during contraction, when they may assume oval, ovoid, vertical and horizontal slits or other pupillary shapes; and much the same state of things is found among the Chameleons, Geckos and Iguanas; and in most of the Snakes.

It is interesting to note, and the observation is probably original with the author, that, so far as his experiments have been carried, the only reptilian pupils that react freely to the

local application of atropine are those of the Crocodilia. The ophidia, amphibia and lacertilia are not affected by eserin or atropia, nor do they react to light and shade as do human eyes.

The color of the iris in the families under consideration is, as every observer knows, infinite in variety. The world over, frogs and toads, tortoises and turtles, lizards and snakes exhibit iridic patterns in every form and color imaginable. Professor Gadow mentions, although he was by no means the first one to observe the fact, that our Box Turtle (*Cistudo carolina*) presents an unusual example of sexual dimorphism; the male has a deep red iris, the female a brown one.

The *ocular excursions* in amphibia Lindsay Johnson finds to be extremely limited and to be confined to retraction of the globe, lateral movements being nil. Chameleons, on the other hand, turn their eyes not only freely but separately in any direction at will, and these movements cover as much as 160 degrees between extreme excursions. Snakes possess a considerable power of ocular movement, their angle of rest being about 70 degrees with the median line. The axial lines of the eyes of Alligators and Crocodiles are directed nearly at 90 degrees to the body line, thus corroborating the author's earlier statement that the lower down the scale of the natural orders the greater the divergence of the eyes.

Using both skiascopy and the direct method of ophthalmoscopy the author found the species examined uniformly slightly hyperopic or practically emmetropic. Our own experience has been the same, except that as regards methods for determining the refraction we decided after a few months of trial to discard the use of the ophthalmoscope except under unusual conditions. It may be that the perfection and general employment in America of skiascopic methods for human subjects (that were first practiced to any extent in England), the facility with which it is taught and learned and its greater reliability had something to do with this choice. And, then, most of us would rather "refract" the eye of a crocodile, snake or "snapping" turtle at one meter than at one centimeter!

Consideration of the *fundus oculi* of amphibia and reptiles forms the chief part of the author's thesis and this section of the work should assuredly be read in its entirety, with comparison of the 46 colored plates that illustrate it, if the student

would carry away the most valuable impressions of this remarkable monograph.

The fundus pictures (with descriptive matter) of the Frogs and Toads are, unfortunately, few in number. The London Zoo has, strange to say, few of these interesting animals in its immense collections, so that Johnson and his artist were naturally limited in their power to reproduce the wonderful eyegrounds of these batrachians. We are glad, consequently, to be able to add the results of our examinations of several South American Frogs not included in his category and to say, briefly, that the results of these observations tally with Dr. Johnson's findings; also that in the case of two of these species —*Rana tigrina* and *Bufo marinus* (examined in British Guiana)—the eyeground details are almost identical.

In both Frogs and Salamanders the *fundi* are entirely different from other vertebrates. There is in all the Frogs so far reported a highly developed vascular system. The most noticeable character is a conspicuous, vertical *median vein* with lateral branches, lying in front of the retina and apparently in the hyaloid membrane. The main trunk of this *vena media* usually passes directly over and appears in bold relief on the whitish background of the perpendicular, elongated optic disk. Johnson refers to a phenomenon familiar to and the admiration of every student of comparative ophthalmoscopy, viz: the stream of large, red, nucleated blood corpuscles that, singly, in doubles or in small masses, slowly passes before the eye of the observer. They are best seen by the upright image with a 15 to 29 D. lens.

The amphibians are without any visible areas of distinct vision (*maculæ* or *foveæ*) and, in that respect differ entirely from Birds, Man and many other vertebrate animals. The background is uniformly gray, grayish, gray-blue or slaty-gray throughout. This coloration is modified by the irregular network of red choroidal vessels that are disposed over the fundus, by the opaque nerve fibers that radiate towards the periphery of the picture and, in some instances, by an immense number of small, colored or whitish dots strewn over the entire eyeground.

Dr. Johnson's hint that other amphibian species not examined by him, may reveal modifications of the foregoing

picture finds justification in several South American varieties observed by the reviewer. For example, in the Frog *Leptodactylus rhodomystax*, the eyegrounds conform, in general, to the average type but in addition one notices, irregularly scattered over about three-fourths of the fundal area, claret colored blotches, which were not noticed in other species of the order so far examined.

In Salamanders and Geckos the disk is round and, in some species at least, uncrossed by retinal vessels.

The ocular fundus in Reptilia presents even a more complex composition, a few of them reminding one of the eyegrounds of the higher vertebrates.

The Lizards—that cosmopolitan family—have nearly all grayish fundi with well marked opaque neural fibers that radiate from the white, spherical and centrally located *Porus opticus*, which is partially or totally obscured by a closely pigmented, black-brown pecten. Snakes have a well-marked system of retinal vessels that, as in Man, pierce the nerve-head.

Lindsay Johnson believes that the pecten "is a secretory organ whose function is to supply nourishment for the inner layers of the retina and the vitreous when the retinal or hyaloid vessels are absent," and gives his reasons for this conclusion. The probable function (or functions) of this remarkable organ, so conspicuous in many of the vertebrate orders, has been discussed back and forth by many comparative physiologists and anatomists in terms upon which lack of space prevents comment here; but it seems to the reviewer that the author has given us the nearest approach to a final decision possible from the data at our disposal.

Finally, we note that the author renews his interpretation of the occurrence of oil-droplets in the retinæ of birds and reptiles and believes they subserve the same purpose to which Lumière put the starch grains in his celebrated autochrome plates, and that the canary yellow coloration of the fovea and macula in Man and the higher apes is proof positive that there are not three but four fundamental colors. Perhaps so. Meantime we may accept the hypothesis that while most vertebrates have a more or less pronounced and developed color sense Fishes are, as Hess maintains, decidedly color-blind.

Dr. Johnson regards his investigations as primarily contributions to physiology, and such they undoubtedly are, but we believe the informed ophthalmologist will find in them something more. We greatly underrate the influence and value of this work if it does not stimulate students of ophthalmology to inquire more than they have done into both the gross and minute anatomy of the ocular apparatus in the lower vertebrates.

CASEY A. WOOD.